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# Editorial

It is with great excitement that we present to you the second issue of the *University of Toronto Medical Journal (UTMJ)* for the 1997-1998 academic year. This year marks the 75th anniversary of publication of the *UTMJ*. In celebration of 75 years of academic and scientific journalism, the *UTMJ* has been re-designed with a fresh look, with the addition of new sections.

In keeping with the mandate of the *UTMJ,* we are pleased to publish two original data articles and three informative reviews of the scientific literature. The feature article is an international piece submitted from St. Andrews Scotland, which provides a detailed discussion of the hereditary breast and ovarian cancer gene, *BRCA1*. This review is followed by an exciting original article that documents *in vivo* gene therapy of IL-10 gene transfection, with the possibility to induce immunosuppression and increase therapeutic efficacy in transplant surgery. The second original paper presents data from the University of Western Ontario which studies medical students' perception of the EFPO (Educating Future Physicians of Ontario) program, in conjunction with the importance of maintaining extracurricular activities during medical school. The final two articles are literature reviews: one of which reviews the role of IL-6 as a future therapeutic modality for neurodegenerative disorders, and the last paper which provides a generalized approach to a patient presenting with acute abdomen.

The sections are dynamic and interesting in this second issue. The News and Views section is the largest it has ever been, which is a reflection of the large student opinion and voice at the University of Toronto. This section presents a variety of interesting articles of academic and personal interest, along with news of current events that occurred at the University of Toronto. The Clinicopathologic Correlation is a complex and challenging presentation that incorporates the essence of modern medicine – the team approach to obtaining a clinical diagnosis. The Quick Diagnosis section tests the knowledge of all the budding nephrologists in the audience, and Morning Report provides a twisting and complex road to the diagnosis of the presentation of headache with an uncommon etiology.

In the first issue (Volume 75, Number 1), From the Archives showcased clippings from the first 25 years of the *UTMJ*. This issue chronicles the Middle Years of the *Journal* from 1948-1972. The Middle Years highlight the outstanding contributions of Nobel Laureate Linus Pauling to the *UTMJ,* along with the remarkable accomplishments of the medical faculty and staff at the University of Toronto in the field of cardiovascular surgery. The last two sections of the *Journal,* Technology Reviews and Book Reviews, provide an overview of the latest trends in scientific software and insight into medical science books.

We are pleased to announce that the *UTMJ* is on-line and can be accessed through our WebSite (http://icarus.med.utoronto.ca/mjweb/www.mjweb.htm). Also, we encourage you, the readers, to send us any comments you may have about the *Journal*. These comments can be e-mailed to the Editors (christine.brezden@utoronto.ca or mike.angel@utoronto.ca) and with your permission, they will be printed in the section entitled Letters to the Editors.

Without further delay, it is with great pleasure that we present Volume 75, Number 2 of the *UTMJ*. We hope you enjoy this issue, as much as we have enjoyed bringing it to you.

Sincerely,

Christine B. Brezden, Ph.D
Michael J. Angel, Ph.D
Editors-In-Chief

Acknowledgements: The *Journal* wishes to thank the following people for their advice and support: Sara Borins, Debra Chang, Chris Graham, Roman Maslcy, and Enrica Veneri.

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# Letter to the Editors

Dear Sir/Madam,

I would like to reply to the article published by Simone and Seidenschmid in the December 1997 issue of your journal entitled, "Infective Endocarditis Prophylaxis for Dental Procedures in Patients with Mitral Valve Prolapse." They cover several interesting points very well but I would like to address some points of concern.

1. Reference is made throughout their article to the 1990 AHA guidelines but no mention is made of the more recent and relevant 1997 guidelines published in JAMA, June 1997.[1] I realize this may have been due to publishing deadlines but feel this is an important omission which your readers should know about.

2. As a result of this, some other information in the article becomes incorrect, primarily the drug dosages which have now been reduced to one pre-operative dose. In the case of Amoxicillin, this is now 2.0 g given orally 1 hour before the procedure. Clindamycin is now given as a single oral dose, 600 mg 1 hour pre-operatively.

3. It is now also recommended that the time interval between appointments where antibiotic prophylaxis is required, be increased to a 9 day minimum. Dental students are advised at the Faculty of Dentistry to extend this time interval where feasible, because of the concern regarding the development of microbial resistance.

4. The 1997 guidlines spell out the dental procedures for which antibiotic prophylaxis is recommended. In general, prophylaxis is recommended for procedures associated with significant bleeding from hard or soft tissues, periodontal surgery, scaling and professional tooth cleaning. What constitutes significant bleeding is left to the dental practitioner's clinical judgment. Allowance is also now made for the provision of post-treatment (up to 4 hours after) prophylaxis should significant unanticipated bleeding occur with a dental procedure.

The net result of these new guidlines should be a decrease in the overall usage of antibiotics for BE [bacterial endocarditis] prophylaxis. These guidlines also raise risk-benefit analysis and emphasize that most cases of BE are not attributable to invasive procedures. Because MVP [mitral valve prolapse] is such a common condition, the management of these patients is discussed at some length and readers are urged to read the original article for additional helpful information. I agree wholeheartedly with the authors' advice that in order for the AHA recommendations to work, it is imperative that physicians and dentists work together to ensure that patients are getting the information they need. They also advise that the primary care-giver, in documenting the presence of MVP in a patient must be determined if it is present with or without regurgitation. If regurgitation is present then BE prophylactic measures should be implemented. Might I add that it would be very helpful to dentists and their MVP patients if patients found at initial examination NOT to have regurgitation, be advised if follow-up examinations are required and if so, what the frequency of these follow-up examinations should be.

I would like to thank the authors for drawing to your readers' attention this common management problem and the range of issues that need to be considered in appropriate management.

Yours truly,

*C. Kilmartin, DDS, MSc., FRCD(C)*
Acting Head and Coordinator of Undergraduate
Programs in Oral Medicine, University of Toronto

## References

1. Dajani AS, *et al.* (1997). Prevention of Bacterial Endocarditis, Recommendations by the American Heart Association. *JAMA.* 277(22): 1794-1801.

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# Familial Breast Cancer: A Review of the Identification, Cloning, Structure and Function of *BRCA1*

James W. E. Paterson BSc., Ph.D Candidate and
C. Michael Steel,* MD, Ph.D, DSc., FRSEDPhil

**Abstract**

Breast cancer has long been known to affect women who have close relatives with the disease more often than the general population. The identification and cloning of a gene, *BRCA1,* that is responsible for early onset breast and ovarian cancer helped explain a number of these cancer predisposed families. Extensive studies of the gene and the protein product have failed to conclusively identify the function in the breast cell leading to carcinogenesis. However, *BRCA1* has been shown to be a tumour suppressor gene. This review article discusses the history of the identification of the gene and the more recent biochemical studies to determine the function and mechanisms of the protein in the breast and ovarian cell.

## *BRCA1* Structure

*BRCA1* is a tumour suppressor gene that is causal for early onset breast and ovarian cancer in susceptible families. The gene, which maps to 17q21,[1-3] was cloned in 1994,[4] and mutations were found to segregate with a cancer predisposing phenotype in *BRCA1* linked families.[4,5] Familial cancers are suspected to account for approximately 5-10% of all breast cancer cases, while *BRCA1* is suspected to account for approximately 40 to 50% of all familial cases.[6] *BRCA1*,[2,7] p53,[8] PTEN[9] and other cancer predisposing genes are responsible for the remaining cases.

*BRCA1* was cloned in 1994 by Miki and coworkers (1994)[4] and initially confirmed by Futreal *et al.*[5] Sequencing affected individuals in breast cancer families confirmed the isolated candi-

Jacomine Robers

*Professor, School of Biomedical Science, University of St. Andrews, St. Andrews, Fife, Scotland

date *BRCA1* sequence. The obtained cDNA coded for a single long open reading frame of 1863 amino acids, with amino terminal similarities to zinc-finger domains; a consensus $Cys_3$-His-$Cys_4$ and other features common to other zinc finger proteins. The genomic structure was found to consist of 22 coding exons, distributed over 100 kb of genomic DNA. Northern analysis revealed a single 7.8 kb transcript, abundant in testis and thymus, but also present in breast and ovary. Besides the single 7.8 kb transcript, they observed a complex splicing pattern in the 5' region of the message.

The promoter region of *BRCA1* is complex, with a genetic duplication resulting in a *BRCA1* pseudogene and promoter region of the *NBR2* gene.[10] Two separate promoters exist for *BRCA1,* each of which promotes transcripts that differ in the first exon (part of the untranslated region).[11] Both of the two promoters are responsive to estrogen, suggesting that *BRCA1* may be involved in hormone signalling pathways.[12] *BRCA1* is responsive to estrogen, although the evidence suggests that this is an indirect and nonspecific response related to changes in the cell cycle and not due to interactions between *BRCA1* control pathways and estrogen response pathways.[13-15] Methylation has also been proposed as a control mechanism for *BRCA1* in sporadic cancers,[16] as well as various post-translational modifications, such as proteolytic cleavage,[17] changes in the phosphorylation state,[18-21] or differential sub-cellular localization.[17,18,22-24] Any of these may be operating independently, or several may act in concert to control the function of the protein.

*BRCA1* mutations are responsible for a group of families that include those with an increased susceptibility to breast cancer alone, or breast and ovarian cancer together,[6,25] and have a slightly increased rate of both prostate and colon cancers.[26] They do not include families with high levels of male breast cancer. The trait is inherited autosomal dominantly as increased predisposition with high penetrance.[27] The risk associated for carriers of mutated alleles is 80-90% for breast cancer and 60% for ovarian cancer during their lifetime. No mutation hot spots have been identified in *BRCA1.* The mutations identified, however, tend to result in truncation of the protein, with only a few missense mutations resulting in amino acid substitutions.[28] These missense mutations cluster to either the amino terminal RING finger domain or the carboxyl terminal BRCT domain, supporting the importance of these two regions in the function of the protein.

*BRCA1* is not mutated in sporadic breast tumours and only rarely mutated in sporadic ovarian cancers.[29,30] Although evidence for the involvement of *BRCA1* in sporadic tumours is convincing,[16,31-34] no mutations have been identified. It is possible that other mechanisms, not detectable by standard mutation screening, may exist for the disruption of function of *BRCA1* in sporadic tumours, such as methylation,[16] large deletion events,[35,36] or decreased expression.[33] However, it is also possible that *BRCA1* does not participate in the formation of sporadic breast cancers at all.

The splice variants have yet to be assigned any biological function, although evidence for their importance has been observed. Reports suggesting that full length *BRCA1* protein (i.e., the protein coded by the entire open reading frame) is toxic to the cells when expressed at anything other than extremely low levels, while a splice variant protein lacking most of exon 11 (*BRCA1*-11b) is not toxic.[24] Additionally, the expression level of the full length protein was found to be similar in all cell lines tested, but *BRCA1*-11b levels were decreased in the most aggressive cell lines, suggesting that the splice variants may serve a tumorigenic function. However, it is not yet possible to detect if the decrease in expression of the splice variant is a cause or an effect of the increased tumorigenicity. Other work also indirectly supports the importance of the splice variants; it has been reported that two different splice variants, lacking the nuclear localization signals, are regularly compartmentalized to the cytosol, but become nuclear by an unidentified mechanism when cells are subjected to scrum starvation.[23] Finally, the number of splice variants reported, encompassing both the coding region and the untranslated regions,[4,11,22-24,37] suggests that they may modulate the function of the protein.

Several different domains have been identified in *BRCA1.* A coding sequence for a RING finger zinc binding domain was identified in the 5' end of the transcript,[4] as well a carboxyl terminal BRCT domain (BRCA1 carboxyl terminal) domain of unknown function.[38] Both regions share the highest conservation between species[39-41] suggesting a functional importance for the gene product. Overall, *BRCA1* shows very poor conservation, however, for a gene of such apparent importance. Other regions identified in the *BRCA1* coding sequence include two functional nuclear localization sequences,[42] a granin consensus sequence,[17] and a *Rad51* interacting domain.[43]

BRCA1 is a tumour suppressor protein. Evidence to support this supposition was apparent even before the gene had been cloned. Tumour suppressor genes require two separate events to abrogate their function.[44,45] The first event is often a localized small mutation event that can be inherited through the germ line and abrogates the function of a single allele. The single allele function is sufficient to give the cell a properly functioning protein. However, a second mutational hit on the other allele, often as large genomic deletion events, completely abolishes the function of the tumour suppressor, allowing a loss of growth control. The chances of accumulating two hits within a single cell on two functional alleles are much smaller than a single hit on any cell to abolish its only functional copy; this results in a predisposition to cancer, often multi focal and early onset, in carriers of mutations.[45]

When genomic deletion events occur, large regions are removed. This is reflected by the loss of markers that are close to the gene of interest. Selecting highly polymorphic markers, such as microsatellite repeats, may allow discrimination between the two copies of the same chromosomal region. Selecting heterozygous markers and looking for the loss of heterozygosity (LOH) in tumour cells then allows the determination of regions deleted in the progression of cancer. Screening large numbers of tumours for this LOH may allow the identification of regions that are often lost and may therefore carry tumour suppressor genes. *BRCA1* has been found to lie in

such an area. Loss of heterozygosity has been observed in both sporadic and familial tumours[31,32,46-54] and, when linkage allowed the determination of the disease causing allele, LOH was always found to affect the wild type allele.[55,56] More concrete evidence for the importance of *BRCA1* in preventing tumour growth is shown by the findings that over expression of *BRCA1* in cells in culture is lethal[24] and antisense inhibition of *BRCA1* results in a reported increase in growth rates specific to breast and ovarian cells,[33] although this has yet to be substantiated by other groups. Work done in our laboratory using antisense-*BRCA1* expression vectors show no changes in either growth rate or hormone sensitivity (manuscript in preparation). Antisense inhibition of mouse NIH-3T3 fibroblasts increased growth rate, soft agar growth, and tumorigenicity,[57] supporting a role for *BRCA1* in tumour suppression.

## History of *BRCA1* and Familial Breast Cancer

It is well established that the presence of breast cancer in first degree relatives (mother or sister) increases one's risk of breast cancer.[58,59] Several studies have quantified the risks associated with first degree relatives with breast cancer. One early study determined that the risk of breast cancer for relatives of breast cancer cases was higher; mothers and sisters of breast cancer cases had 3.2 fold and 2.2 fold increased risk respectively, while a 9.9 fold for sisters of cases whose mother also had the disease was reported.[60] It was noted that the increased risk applied only to first degree relatives (i.e., mothers, sisters) and that substantial increases in risk could not be proved for more distant relatives. Another study confirmed the increased risk for relatives of cancer cases, however, with lower estimates.[61] The lower estimates may just be a reflection of the design of the study and differences in the population.[62]

The study undertaken by Schwartz and coworkers (1985)[62] linked the age of onset of the index case to risk of cancer in first degree relatives, an observation that supports the later findings that familial cancers tend to show an early onset. It was noted that sisters of cases diagnosed before age 40 were at a higher risk than sisters of cases diagnosed after age 40. Women related to patients with later onset disease also had an increased risk, but the risk was lower and onset of disease in daughter or sister tended to be later. A set of studies by Anderson (1972 - 1977)[63-66] and by Ottman and colleagues (1986)[67] suggested that different characteristics of breast cancer (i.e., bilaterality and age of onset) also increased the risk of breast cancer in relatives, each factor modifying the risk individually.

These studies all combined to suggest that breast cancer, particularly early onset breast cancer, was in some way familial; all the studies showed that risk of breast cancer is increased if members of the family had breast cancer, with more closely related relatives affected by breast cancer, and the severity of the index case (i.e., bilaterality, early onset). However, they did not prove that breast cancer was a heritable disease (i.e., passed through the family), but only that clustering occurs. These studies assigned a more precise estimate of the risk associated with familial breast cancer, but could not show the mode of inheritance. The causal factor(s) could be a single gene, an array of genes each modifying the risk, or might be unrelated to genetics, attributable to a shared environment, or any combination of the above.

Studying many families that show the trait by looking for the transmission patterns between generations, is necessary to establish if a disease is genetic, or the dominance of a genetic trait. For breast cancer this is confounded by two factors; the high numbers of sporadic cases that occur in most populations and the likelihood that some "at risk" individuals would not develop cancer in their lifetime ('incomplete penetrance'). However, the search for the causal factors for familial clustering of breast cancer was undertaken. To detect the causal factors, families that had breast cancer were collected and studied.

These studies began to detect the mode of inheritance for many families; first, a genetic basis was suggested in many families,[68] but not the genetic mechanism; the next studies suggested a single gene effect could account for familial clustering of the disease.[69] Finally, a genetic mechanism for breast cancer clustering was identified to account for breast and ovarian cancers.[27] The study identified a large number of nuclear families for segregation analysis with further analysis of a single very large kindred with familial breast cancer. The analysis they undertook suggested that a single dominantly acting gene, without any cultural or polygenetic effects, would account for breast cancer in these families. From these results, it was suggested that breast cancer families are a result of a single gene disorder. Combined with the previous studies, which suggested that early onset and bilaterality were also associated with familial clustering, the early onset breast cancer syndrome was identified in these families. Although other studies have suggested that the gene may be recessive,[70] the most convincing analysis suggests that a dominant gene is most likely.[27]

The identification of a single or a few genes for familial clustering prompted a concerted effort to identify the causal gene; it was hoped that the gene responsible for early onset familial breast cancer may be essential for tumorigenesis in sporadic breast cancer (that comprises most cases).[71] This search for the gene was complicated by some epidemiologic facets of the disease; breast cancer is common, and only a few of the cases in the population were demonstrably inherited.[27] Despite these problems, in 1990, a gene for the early onset familial breast cancer syndrome was mapped to the long arm of chromosome 17, in band 21 (17q21).[71] Many plausible candidate genes had already been identified in this region, including: a truncated *her2* gene (epidermal growth factor receptor (EGFr)); *edhb17* (estradiol-17 dehydrogenase gene); *hox2* (homeobox 2 gene); *nm23* (a gene associated with lymph node metastasis in breast carcinomas); *rara* (retinoic acid receptor gene); and *wnt3* (homologue of an integration site activated by the mouse mammary tumour virus in mice).

Further mapping confirmed[72] and narrowed the region[1,73-76]

of *BRCA1* to be within a region bounded by D17S1321 and D17S1325.[3] Several potential genes for the locus were also eliminated by these mapping studies, including *rara, her2 (erbb2), gh,* thyroid hormone receptor A1, and *igfbp4.*[25,74,75]

## *BRCA1* Function

The exact biochemical and cellular functions of *BRCA1* remain elusive, as do some basic characteristics, such as its sub-cellular localization. The preponderance of evidence suggests that *BRCA1* is localized to the nucleus,[18,19,24,43,77-81] with a nuclear punctate pattern appearing during S and M phases.[19,43,79] However, it has also been suggested that *BRCA1* is a granin, initially targeted extracellularly and proteolytically cleaved to activate its function.[17] These extracellular protein fragments may become localized to the nucleus, however, this would be by a secondary mechanism involving transport following binding to membrane receptors.[82]

The cloning of *BRCA1* has not allowed the elucidation of the function of the protein. Although it is generally accepted that *BRCA1* is a tumour suppressor, how this suppressor function is mediated still remains largely an enigma. However, the cloning of the gene has allowed more careful examination of various aspects of the function and steps have been made to understand the mechanisms by which the protein functions.

*BRCA1* serves a complex set of functions in the cell that may or may not be linked to a common biochemical mechanism. In humans, the protein is mainly involved with progression of breast and ovarian cancers, with small effect on the progression of colon and prostate cancers. This suggests that the protein does not serve an essential role. Supporting this, a report has been made of an apparently normal individual (with breast cancer) who has inherited two mutated copies of the gene.[83] However, in mice this is not so. Targeted disruption of *BRCA1* results in *in utero* death, with gross abnormalities to many structures, and cells lacking *BRCA1* are unable to grow.[84-86] Although targeted disruption of *BRCA1* results in death at a variety of stages of development, from 5 days to 12 days, all are lethal. Although normal *BRCA1* function is essential in the mouse, it appears to be less so in humans. The observed phenotypes suggest that *BRCA1* serves functions in both development and cancer progression. Unfortunately, mouse models do not allow the determination of the effects of *BRCA1* on normal adult mammary tissue; heterozygous mice are viable and are completely normal, without susceptibility to any cancers.

### A. *BRCA1* in DNA Repair

Several pieces of evidence suggest that *BRCA1* may be involved in the recognition and repair of DNA lesions. However, the exact mechanisms have yet to be determined, nor have the effects of *BRCA1* DNA damage recognition been defined. *BRCA1* has been specifically associated with DNA repair by homologous recombination,[43,87] supported primarily by the interaction of *BRCA1* with *Rad51*,[43] a protein involved with the homologous pairing of DNA during the process of recombination and recombinational repair.[88,89] The interaction of *Rad51* and *BRCA1* was first identified through observations of a discrete nuclear punctate staining pattern for *BRCA1* during S and M phases of the cell cycle,[43,79] a pattern that occurs for *Rad51.* Although the interaction is specific, the reason for the interaction has not been identified. Reports have been made that *BRCA1* undergoes dramatic changes in phosphorylation and subnuclear localization in response to DNA damage.[20] The changes in the localization observed for *BRCA1* also occur for *Rad51,* suggesting that they may have a physiological interaction that is responsive to DNA damage. This interaction of *Rad51* and *BRCA1* however cannot be the sole function for *BRCA1; BRCA1* is highly expressed during spermiogenesis[90] while *Rad51* expression is shut off during the same period.[91]

Both *Rad51* and *BRCA1* nullizygous mice have severe embryogenesis disruption and die *in utero,* showing that they may be related to similar pathways. However, the phenotype of the lethality is not the same for both genes; *BRCA1* loss of function results in death near E7.5[85,86] or even later at E11,[84] while *Rad51* nullizygosity results in death as early as the morula/blastocyst stage.[92,93] Both *BRCA1* and *Rad51* nullizygotes share other similar aspects including the inability to grow in tissue culture and a partial rescue of the phenotype when introduced into mice with p53 and $p21^{Waf1/CIP1}$ null background.[86,92,94] This apparent block on cell growth may only be active in fetal cells, as disruption of *BRCA1* in adult cells has been reported to increase cell growth[33] and tumorigenicity.[57]

Further evidence for the participation of *BRCA1* in DNA damage repair and recognition is the presence of a BRCT domain,[38] which is common in proteins that participate in DNA repair and metabolism.[95-97] However, this evidence is again circumstantial. The BRCT domain has had no function directly attributed to it, except in a few cases.[95,96] The BRCT domain seems important for protein-protein interactions such as between p53 and 53BP1,[38] *BRCA1* with the RNA polymerase II holoenzyme,[98] and XRCC4 with DNA ligase IV.[99] Such interactions have been proposed as a mechanism for the recruitment of members of the DNA damage repair family to the site of repair through BRCT domain interactions, such as XRCC4 recruitment of a suitable DNA ligase to DNA PK repair complexes.[99] However, as *BRCA1* is co-localized with *Rad51,* but not directly at the break point,[43,89] it is unlikely that it can participate directly with DNA damage repair at the site of the lesion.

The final evidence supporting the participation of *BRCA1* in DNA damage response pathways are interactions reported between *BRCA1* and p53 pathways. *BRCA1* nullizygosity introduced into a p53 null background partially rescues the *BRCA1* lethal phenotype, extending the time of death from E7.5 up to E11.[86,94] This suggests that *BRCA1* may be responsible for DNA damage sensing and repair and when its function is lost, DNA damage accumulates and p53 responsive pathways cause cellular arrest and allows cell death to occur. Loss of p53 function in these cells then allows the cells to continue dividing with damage until genomic stability is compromised sufficiently to result in cell death. Although this link between the pathways is tenuous, clinical observations support a link between *BRCA1* associated tumorigenesis and p53. In a recent study, p53 was mutated in all the tumours of all *BRCA1*

mutation carriers,[100] suggesting the loss of p53 is an absolute requirement for the progression of cancer. Additionally, the spectrum of mutation was not as expected for an unselected series of sporadic breast cancers; mutations were almost exclusively in exon 5 of p53 (the amino end of the DNA binding domain of p53), mutations that are common to sporadic breast cancer were not common in *BRCA1* associated cancers, and in several cases, multiple mutations were identified in a single allele of p53, sometimes as many as four. This hypermutability of p53 was not a result of increased general mutation rates as other genes did not show increased mutability, nor did other regions of p53. The observation of multiple mutations within single alleles of p53 is interesting; a single event is enough to impair p53 function, so multiple events should not provide a growth advantage to cells.

As well as p53 involvement, a recent report has shown $p21^{Waf1/CIP1}$ activation by *BRCA1* to induce a $G_1$ to S phase cell cycle block.[101] This observation concurs with observations of the cell cycle regulation of *BRCA1*; although expression seems maximal after this checkpoint, it is induced in late $G_1$.[19,102-104] The interaction between $p21^{Waf1/CIP1}$ does suggest that a link exists between *BRCA1* and cell cycle checkpoint control, suggesting that *BRCA1* may be more than a simple DNA repair protein. It has been proposed that *BRCA1* is a guardian of genomic integrity,[97] explaining why mutations in this gene are not found in sporadic cancers.

### B. *BRCA1* in Cell Cycle Control

*BRCA1* is a protein whose expression is closely linked to the cell cycle, both in expression level and phosphorylation status.[19,21,102-104] Various cell cycle regulated and regulatory proteins, such as cdc2, cdk2, cdk4, cyclin A, cyclin B, cyclin B1, cyclin D, cyclin D1, and E2F-4, interact with *BRCA1*,[19,23] mainly modifying the phosphorylation state. Furthermore, an association between *BRCA1* and erbB/neu proteins (the EGFR family of receptor tyrosine kinases) has been proposed[21] such that activated tyrosine kinase receptors tyrosine hypophosphorylate *BRCA1*, resulting in inactivation of the protein. This hypophosphorylation of *BRCA1* leads to a $G_2$/M cell cycle arrest.[21] The proposal for a $G_2$/M arrest has been supported by observations made with a *BRCA1* mutant that abrogates such a checkpoint.[105] Several reports have been made suggesting that *BRCA1* mediates a $G_1$/S phase checkpoint.[101,103] The checkpoint may be activated through the transcriptional activation of $p21^{Waf1/CIP1}$ and p53 independently.[101]

Further evidence for a role in the control of the cell cycle is suggested by observations of changes in the subnuclear localization during the cell cycle. *BRCA1* is observed as a diffuse, weak, nuclear staining in cells in most stages of the cell cycle. However, during S and M phases, a nuclear punctate pattern appears.[43,79] This dramatic change in the localization is also modified by the presence of DNA damage.[20] DNA damage results in the release of *BRCA1* from the complexes with a concurrent change of phosphorylation state and the accumulation of *BRCA1* on PCNA containing structures suggests an interaction between *BRCA1* and damaged replicating DNA. Evidence is strong that *BRCA1* does affect the cell cycle; reduced expression is associated with highly proliferative cells *in vivo*[106] and low *BRCA1* levels increase growth rates;[33,57] high expression of *BRCA1* is toxic to cells[24,34] and even affects yeast cells[107] which do not have any identifiable *BRCA1* homologue. *BRCA1* has been proposed to be a DNA binding transcription activator,[4] supported by transcriptional activation by GAL4/*BRCA1* fusions[108,109] and the association of *BRCA1* with the RNA polymerase II holoenzyme.[98] The same domain, the BRCT domain, is both the transcriptional activator and the RNA polymerase II interacting domain, suggesting that *BRCA1* may recruit the transcriptional machinery to target promoters through interaction with DNA or other proteins. Such evidence suggests a mechanism by which *BRCA1* may mediate control over the cell cycle.

### C. Development and Differentiation

*BRCA1* appears to serve a role in development and differentiation. The nullizygous mouse models that have been developed show that such a function is essential for cellular survival during embryogenesis.[84-86,94] The protein is expressed throughout all tissues of the developing mouse, particularly those that are rapidly proliferating and undergoing differentiation.[110] This is seen during pregnancy and during lactation in the mouse, when high levels of *BRCA1* are expressed during the rapid hormonally induced growth associated with lactation and differentiation of the mammary gland.[110,111] Observations of the expression of *BRCA1* in human spermatocytes support a similar role in differentiation in humans.[90]

## Medical Relevance of *BRCA1*

Beyond screening individuals from families with high risk for cancer, *BRCA1* has some potential for use as a treatment. With the observed toxicity of over-expression of *BRCA1*,[24,34] clinical trials have been undertaken to introduce wild type *BRCA1* to ovarian tumours using a retroviral vector.[112] Such a treatment strategy has met with limited success, however it is limited by the delivery mechanisms that are available to surface tumours, and is therefore not suitable for the treatment of breast tumours. If *BRCA1* is a mediator of genomic stability,[97] this treatment strategy may be ill-advised. By stabilizing the tumour genome in a highly proliferative state, many of the cells that would have died of genomic instability could survive.

Other than direct treatment of tumours using gene therapy, careful study of *BRCA1* and tumour phenotypes may result in improved traditional treatment of *BRCA1*-associated tumours. Mutation status of *BRCA1* has also been noted to be correlated with several histopathological parameters that collectively determine the grade of the tumour.[69,113-115] *BRCA1*-associated tumours tend to be high grade, invasive, and highly proliferative. Such changes are intuitively associated with a poorer prognosis, however *BRCA1* tumours may be more drug-responsive than their unmutated counterparts.[14,15,116] This drug sensitivity may be a result of increased genomic instability in these tumours (if *BRCA1* is a mediator of genomic stability[97]) or may be due to higher growth rates resulting in a generalized increase of toxicity of

these tumours. Further study should help to define this, and allow a better treatment strategy for *BRCA1*-associated tumours. In addition, *BRCA1* affects the clinical outcome of patients.[114,117-126] Many *BRCA1*-associated cancer cases have a better prognosis than their sporadic counterparts; the reason for this is still unclear and may be a result of *BRCA1* directly or from the tumour phenotype that *BRCA1* tumours assume.

## Summary

BRCA1 is an apparently complex gene that participates only in familial breast and ovarian cancer. Although it is a tumour suppressor, it is also essential for the normal growth and development of fetal cells. *BRCA1* has been suggested to be involved with DNA damage and repair, in cell cycle regulation, and in differentiation of cells. If these functions are united under a single mechanism or pathway, or if they are all served by different pathways, remains to be determined. Since the cloning of *BRCA1* in 1994, much has been learned about the function of the gene. However, much more still has to be understood. The size of the protein coded by the *BRCA1* gene and the variety of transcripts argues for a complexity of function and regulation that will confound attempts at understanding for years to come.

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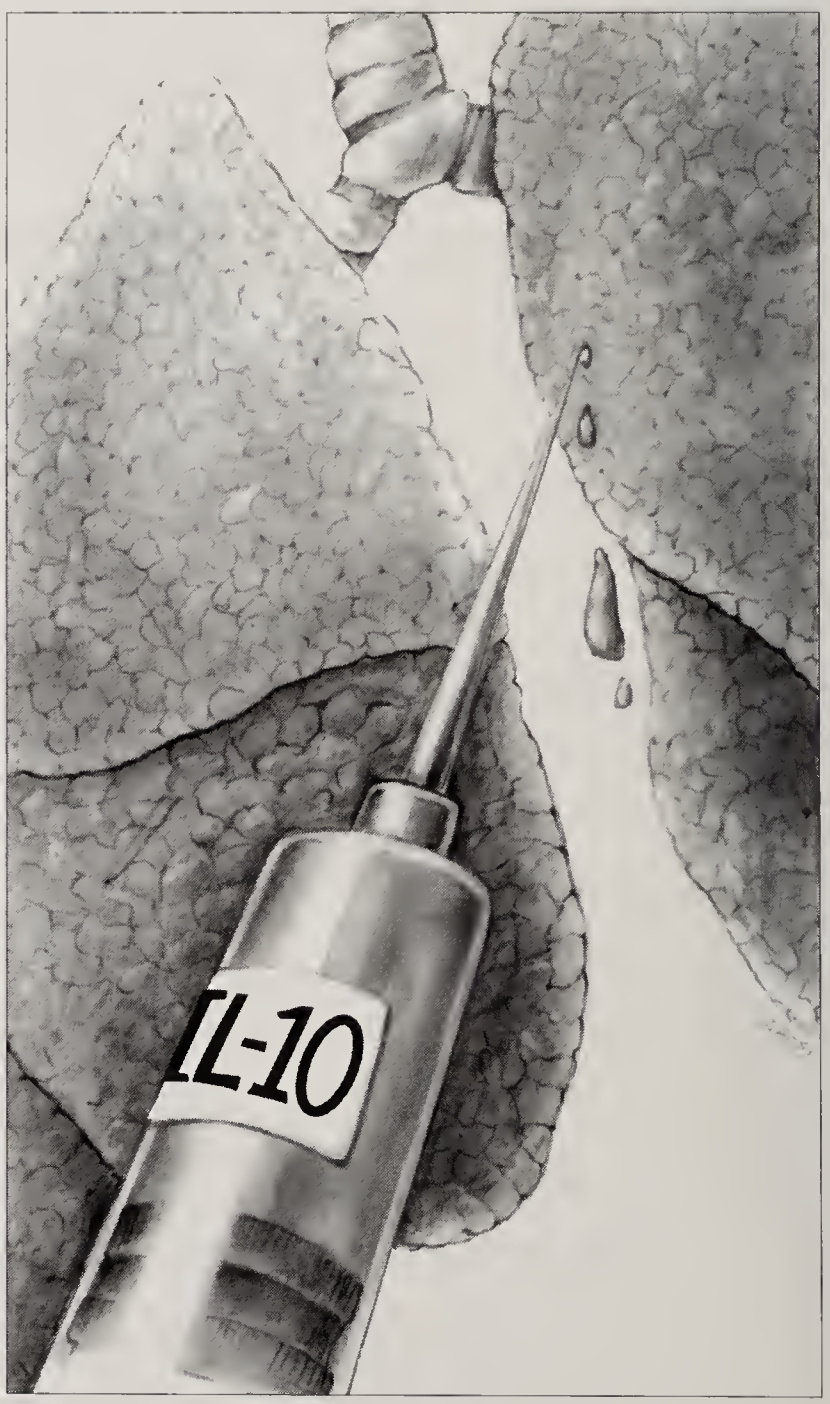
# Adenoviral-mediated Interleukin-10 Gene Transfection: Optimal Dosing in a Rat Model

Ian D. Bookman, BSc. (0T0), Stephen D. Cassivi, MD, Annette Boehler, MD, Mingyao Liu, MD and Shaf Keshavjee, MD, MSc., FRCSC

**Abstract**

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that has recently been suggested to have protective activity against both the oxidative injury of ischemia-reperfusion and the destructive damage of chronic rejection in lung transplantation. In a lead up to therapeutic studies using the IL-10 gene, the transfection efficacy of a replication-deficient adenoviral vector expressing human IL-10 was investigated. To assess optimal dosing, three dosages of the vector-gene construct were administered to rats by intramuscular injection. Human IL-10 transgene expression was measured from plasma samples on days 1, 7, and 14 post-injection. Results showed a dose-dependent pattern of expression, with peak levels at day 1 and declining levels thereafter. These findings demonstrate that intramuscular adenoviral IL-10 gene transfer provides measurable levels of transgene expression in plasma. The rat model of adenoviral-mediated IL-10 gene transfer, thus characterized, provides the basis for further investigation into the physiologic effects and therapeutic potential of IL-10 in an *in vivo* lung transplantation model.




Jennifer Bosy

## Introduction

Lung transplantation provides life-saving therapy for patients with end-stage lung disease; however, difficulties

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remain in obtaining and maintaining optimal graft function following transplantation. During the early postoperative period, lung reperfusion injury contributes significantly to patient morbidity as evidenced in increased ventilatory requirements and prolonged intensive care unit stays.[1] In the long term, survival is limited mainly by chronic allograft rejection in the form of bronchiolitis obliterans which is characterized by a progressive fibrous scarring of the small airways.[2] Together, the processes of reperfusion injury and chronic rejection are the major contributors to patient morbidity and mortality. A rat model developed to study chronic allograft rejection has shown that an immunological reaction may play a key role in this process, and the administration of interleukin-10 (IL-10) may inhibit its development.[3,4]

IL-10 is a soluble protein possessing several immunosuppressant and anti-inflammatory effects. Among these, IL-10 inhibits production of several proinflammatory molecules including IL-1, IL-2, IL-3, IL-6, IL-8, IFNγ, TNF-α and down-regulates immune surface molecule expression on various cell types *in vitro*.[5-9] *In vivo,* IL-10 has been shown to inhibit allogeneic proliferative and cytotoxic T cell responses which suggests a potential clinical use in inducing and maintaining allograft tolerance following organ transplantation.[10] Further *in vivo* studies have investigated the anti-inflammatory and immunologic properties of IL-10 in models of endotoxemia, autoimmune diseases, and allergen-induced lung inflammation.[11-13]

Nearly all *in vivo* studies to date, however, use recombinant IL-10.[10-12] Recombinant cytokines including IL-10 are known to be short-lived and have limited access to the tissue interstitium *in vivo.* It has recently been shown that cytokine gene transfer *in vivo* by adenoviral vector-based techniques can achieve relatively high transfection efficiency and may be used to achieve transient but measurable transgene expression at different tissue sites.[14,15] These features make adenoviral vectors an attractive vehicle for IL-10 gene therapy in clinical settings such as organ transplantation. The aims of this study were to: 1) determine the dose of IL-10 adenovirus construct which expresses measurable IL-10 protein in a rat model; 2) investigate the relationship between IL-10 adenoviral dose and transgene expression; 3) determine the time course of IL-10 transgene expression.

## Material and Methods

Male Lewis rats (300-350g; Harlan, Indianapolis, Indiana) were randomly assigned to one of four groups (n=12) according to the dose of the vector to be administered. (1) High Dose: $1x10^{10}$ pfu; (2) Mid Dose: $5x10^{9}$ pfu; (4) Low Dose: $1x10^{9}$ pfu; (4) Control: phosphate buffered saline (PBS). An E1-deleted, replication-deficient Type 5 adenovirus containing the human IL-10 (hIL-10) gene with a Roux Sarcoma Virus (RSV) promoter (AdE-1RSVhIL-10; University of Iowa Gene Vector Core, Iowa City, Iowa) was administered intramuscularly (i.m.) following anaesthesia comprising of ketamine (Rogar, London, Ontario) and acepromazine (Ayerst, Montreal, Quebec). Tail vein blood samples were then collected on days 1, 7, and 14. Serum concentrations of hIL-10 protein were measured using the ELISA technique (Biosource International, Camarillo, CA). All samples and controls were pipetted into wells coated with antibodies specific for hIL-10. A biotinylated second antibody was added to the wells, allowing the hIL-10 to bind simultaneously to both antibodies during incubation. Next, streptavidin-peroxidase was added, and this enzyme was bound to the second antibody, thus completing the four-member sandwich. A substrate solution was then mixed in to produce colour. The intensity of this colour was measured by a spectrometer and was directly proportional to the concentration of hIL-10 present in the original specimens.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institute of Health (NIH publication No. 85-23, revised 1985) and the "Guide to the Care and Use of Experimental Animals" formulated by the Canadian Council on Animal Care.

Statistical analysis of the data was performed using a mixed factorial design to compare the effects of both dose and time on IL-10 transgene expression. A Student Newman-Keuls test was used to determine statistically significant differences between groups.

## Results

In all three dosing levels, a peak value of hIL-10 was observed at day 1 with decreases notable in all groups by day 7 and virtually undetectable levels at day 14. The high and medium dosages produced levels of hIL-10 which were over 14 and 5 times higher than control levels respectively. Both of these differences were statistically significant ($p<0.01$) at the day 1 time point (Figure 1). The pattern of IL-10 expression showed a dependent relationship with the level of IL-10 adenoviral dose administered. As the dose of IL-10 adenovirus increased, the levels of IL-10 protein also increased (Figure 2). No side effects were observed in any of the animals throughout the study period. One animal died during anaesthesia.

## Discussion

IL-10 has been shown to be a useful anti-inflammatory agent and potent suppressor of various cellular immune responses.[16] In the setting of lung transplantation, such qualities enable IL-10 to play a preventative role against both the oxidative injury of ischemia-reperfusion and the development of chronic graft rejection, the leading causes of morbidity and mortality in lung transplantation patients.[17,18] In using recombinant IL-10, studies to date have suggested potential benefit. However, the short half-life of recombinant IL-10 necessitates the implantation of a minipump for frequent dosing; both the clinical and economic feasibility of this approach have been questioned. Sustained increased levels are potentially achievable though by hIL-10 gene transfer.

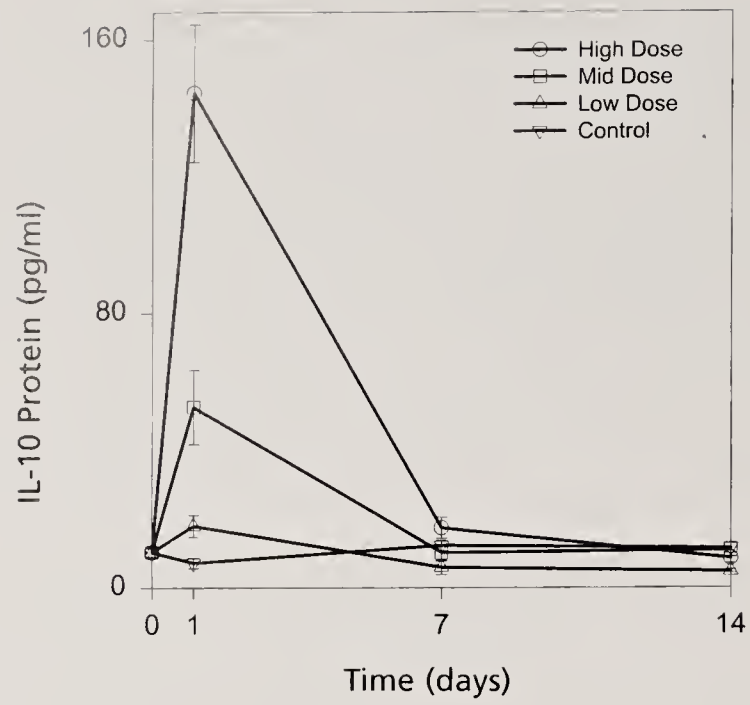


FIGURE 1. Dose Dependent Transgene Expression. *Adenoviral-mediated IL-10 expression levels peak at day 1 and significantly decrease thereafter. Both high dose and mid dose levels of IL-10 adenovirus provide significantly increased levels of IL-10 transgene expression.*

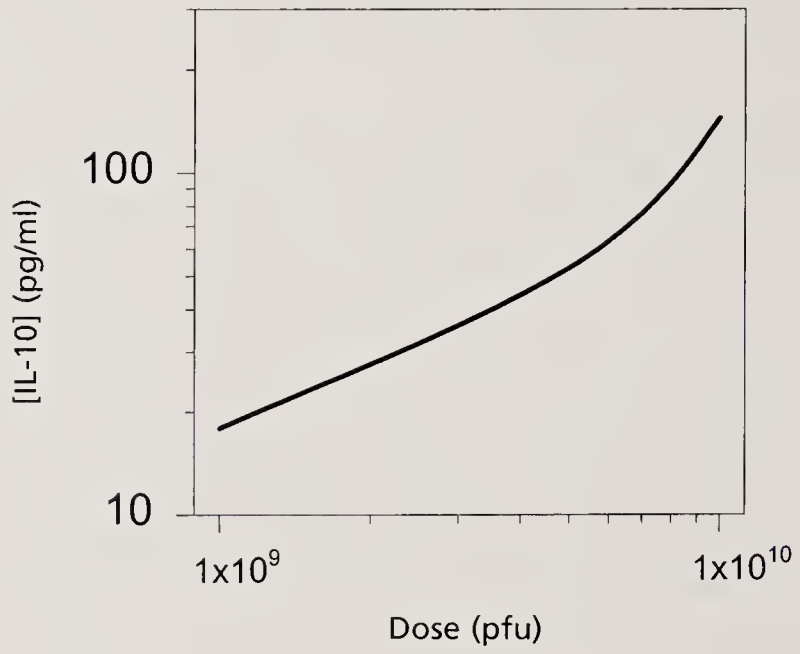


FIGURE 2. Dose Dependent Relationship. *IL-10 transgene expression is dependent on the administered dose of adenoviral IL-10 construct.*

In this study, we investigated transgene expression of IL-10 administration by adenoviral-mediated gene transfer. With a reproducible peak of hIL-10 expression at day 1, adenoviral-mediated gene transfer was shown to provide measurable, dose-dependant levels of transgene expression. Both high dose and mid dose groups showed significantly increased levels of IL-10 transgene expression at day 1 as compared to control and low dose groups.

The possible outcomes from injecting doses of adenoviral IL-10 beyond the tested range must be considered. At doses higher than $1x10^{10}$ pfu, protein expression may either further increase or else plateau as a result of saturating the rate-limiting process of protein expression in the rat cells. In the low dose group, measurable protein was not significantly increased at the day 1 time point as compared to the control. From this result we can conclude that there are no adenoviral doses less than $1x10^{9}$ pfu that express measurable amounts of hIL-10 protein significantly greater than the control.

The levels of transgene expression achieved in this study are somewhat lower than predicted, based on previous cytokine gene transfer studies.[19-21] These decreased levels are potentially explained by cross-reactions between the native rat and transfected human isoforms of IL-10, due to their relative homology, at the transcription, translation, or protein level in the rat.[22] Furthermore, rat IL-10 may interfere with the ELISA assay which is specific for human IL-10, though these interactions have not been previously documented. No cross-reactivity between the currently available ELISA kit and rat serum has been documented.

While detectable levels completely disappeared by day 14, they may still be well above baseline, as the detection threshold of the ELISA technique used is approximately 16pg/ml. Therefore transgene expression of IL-10 may be present for periods of 7-14 days post-transfection or longer, and require more sensitive assays to demonstrate this expression. Lower concentration levels of IL-10 may still confer therapeutic effects, and will need to be determined in subsequent investigations.

Studies, completed in our laboratory, have shown that the effects of immunosuppression can both increase and prolong adenoviral-mediated transgene expression.[23] Having characterized the dosing levels and efficiency of adenoviral-mediated IL-10 gene transfer, it is now possible to investigate the combined effects of immunosuppression and adenoviral-mediated gene transfer. This present study provides the foundation for further research into the beneficial uses of the adenoviral IL-10 gene construct in the clinical setting.

## Acknowledgements

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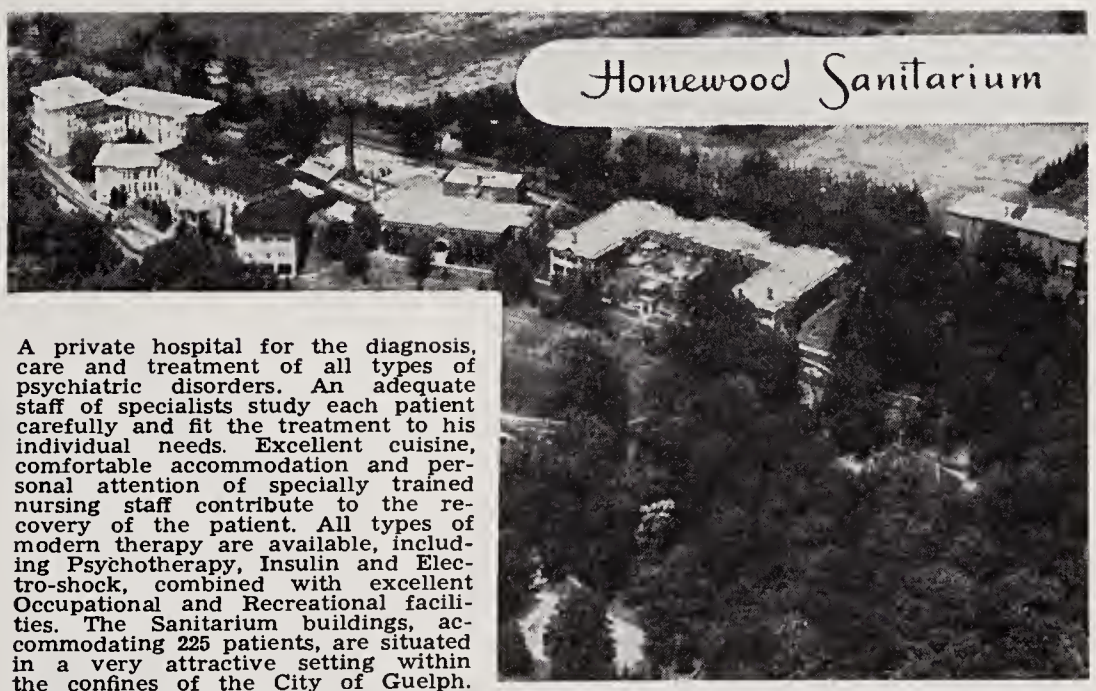


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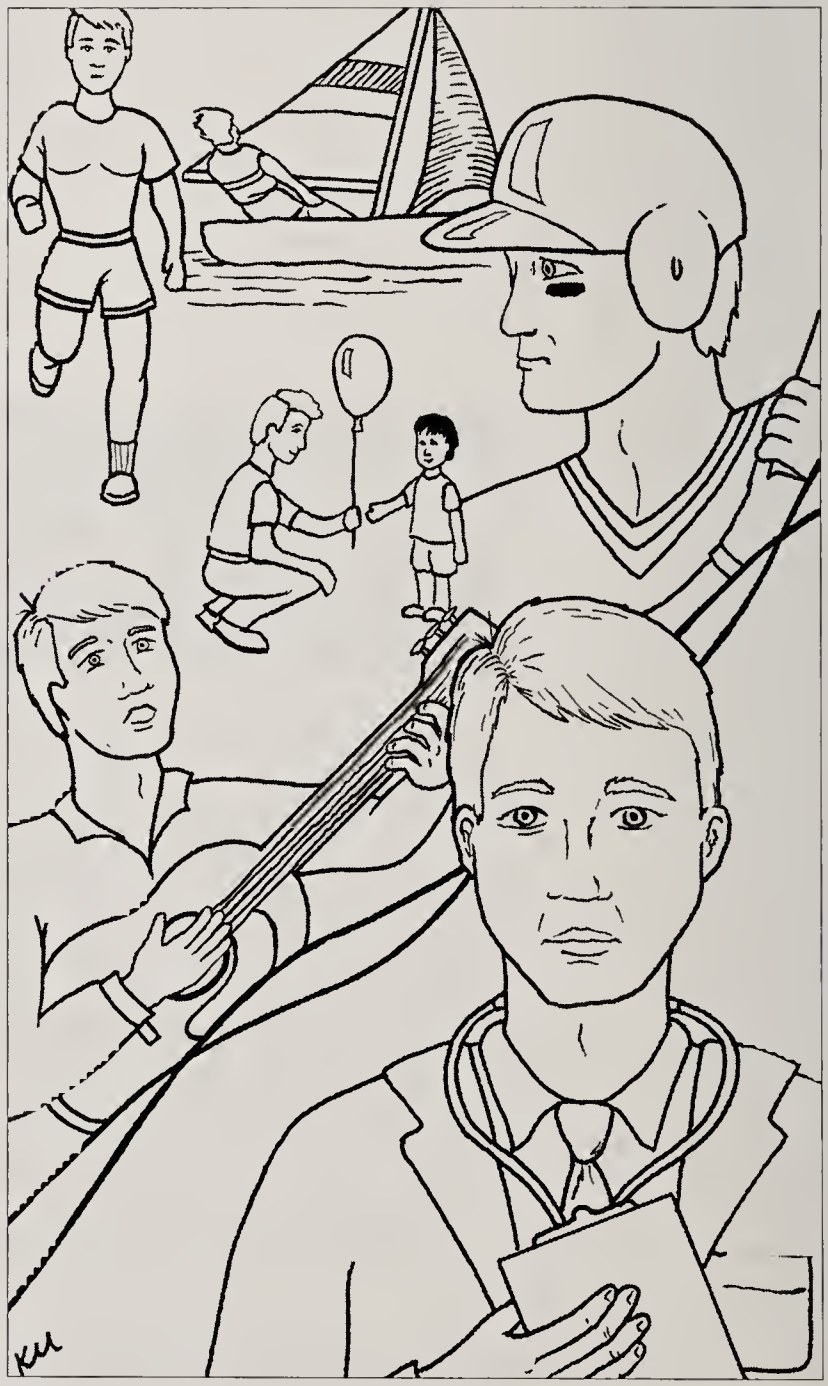
# The Potential Educational Value of Extracurricular Activities in the Context of the Roles of the EFPO Physician

Bindu Kumar, BSc., Nimesh Desai, BSc. and Wayne Weston,* MD

**Abstract**

The Educating Future Physicians for Ontario (EFPO) project has been influential in the evolution of new medical school curricula, attempting to make education more reflective of the diverse needs of the community. Students have, as well, developed their own approach to addressing the needs of Ontario society by taking a proactive approach to addressing those issues inadequately represented in the curriculum through involvement in extracurricular activity. The extent of such involvement and students' perceptions of EFPO as a vehicle in modifying medical curricula remain to be defined. In the present study, first year medical students at the University of Western Ontario (UWO) were surveyed to determine 1) their level of extracurricular involvement and 2) their perceptions of EFPO. The median hours of extracurricular involvement were 3.5/week (n=67). Ninety percent felt that extracurricular involvement was important to their life in medical school (n=62), with 58% of students indicating that they joined an extracurricular activity to explore a subject inadequately covered in the curriculum (n=68). While 84% felt that EFPO should play a role in their medical education, 70% indicated that, to their knowledge, EFPO had played a limited to no role thus far. These findings suggest that strategies aimed at promoting EFPO more efficiently may be highly desirable and that EFPO can further investigate extracurricular activity as a component of medical education.



Kevin Millar

*EFPO Site Coordinator, Faculty of Medicine, University of Western Ontario

## Introduction

The Educating Future Physicians for Ontario (EFPO) project was initiated by the Associated Medical Services, the Ministry of Health of Ontario, and the five Ontario medical schools. The ultimate goal of the project is "to make medical education more responsive to the evolving needs of Ontario society."[1] To this end, the EFPO project explored the needs of specific sectors of the community using focus groups and documented the public's expectations of physicians. This cooperative effort by educators, community groups, and members of the medical profession led to the identification of eight physician roles which were deemed to reflect these expectations: Medical Expert/Clinical Decision Maker; Communicator (Educator/Humanist/Healer); Health Advocate; Learner/Scholar; Collaborator; Gatekeeper/Resource Manager/Steward; Scientist and Physician as Person. The advances in medical education brought about by the EFPO project have facilitated the development of new educational curricula at all five Ontario medical schools (reviewed in 1).

Through its working groups, EFPO has addressed the imbalance between what students are taught and what they will need to know as physicians.[2] Figure 1 outlines EFPO's attempt to assess the needs of the community and make recommendations for the revision of medical curricula in order to address this imbalance. We propose that students have taken steps toward compensating for this imbalance by sensing those issues that are inadequately addressed or omitted from the curriculum, a strategy not acknowledged by EFPO thus far. By creating extracurricular interest groups that reflect their ideas and attitudes related to medicine, students are expanding their educational experience beyond conventional curriculum and Problem Based Learning. Currently there is no literature available describing the role of extracurricular activities in medical education. In addition, students' perceptions of EFPO as a modifier of medical education remains to be defined. Furthermore, EFPO has not acknowledged the strategies students have employed to supplement their curriculum to further reflect the expectations of future physicians. This study assesses the level of involvement of medical students in extracurricular activities and their perceptions of the EFPO project.

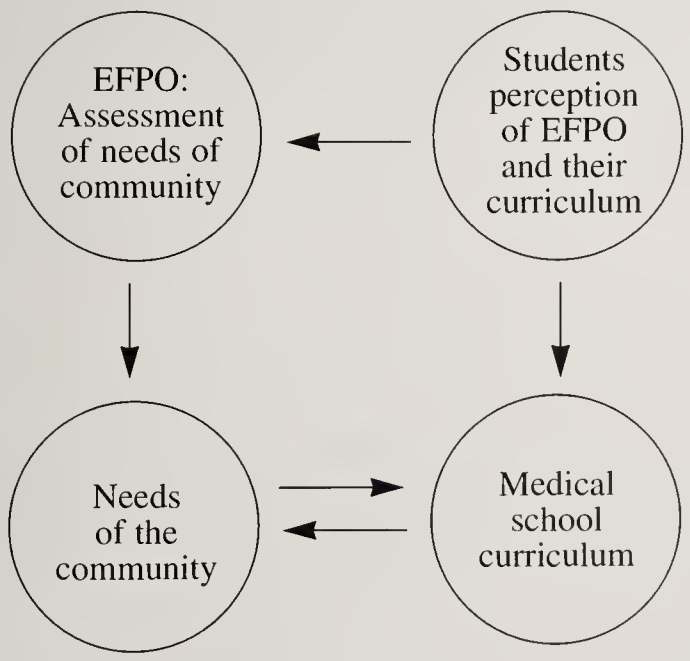

EFPO: Assessment of needs of community
Students perception of EFPO and their curriculum
Needs of the community
Medical school curriculum

FIGURE 1. *Collaborative Model of Medical Education including the role of students.*

## Methods

In order to assess student opinions and level of student involvement, students were surveyed with both multiple choice and written type questions. Our study population was comprised of the University of Western Ontario first year medical school class. Of the 101 students in the first year class, 79 students were present on the day the survey was administered and 73 surveys were returned (return rate=92%). Ethics approval was obtained for research on medical students from the University of Western Ontario, Faculty of Medicine. The surveys were anonymous and participation was voluntary. The data was tabulated and analyzed using EpiInfo 6.0.

## Results

The median hours of extracurricular involvement for a first year medical student at Western was 3.5 hours/week (range=0 to 30 hours/week, n=67). The mean was 5.7 ± 6.3 hours. As seen in Table 1, extreme values resulted in a skewed distribution. Of those who responded to this question, about 15% spent over ten hours a week on extracurricular activities, while 39% said they spent less than two hours per week on extracurricular activities. Ninety percent (n=62) stated that extracurricular involvement was very important to their life in medical school.

**Table 1**
**How many hours a week do you usually spend on extracurricular activities?**

| Hours per Week | % of Respondents (n=67) |
|---|---|
| ≤ 2 hours | 39 |
| > 2 hours and ≤ 5 hours | 33 |
| > 5 hours and ≤ 10 hours | 13 |
| > 10 hours | 15 |
| Mean | 5.7 ± 6.3 hours |
| Median | 3.5 hours |

A majority of students (58%, n=48) stated that they joined an extracurricular activity to learn about subjects that were not taught in their current medical school curriculum (Table 2). Written responses of explanation were compiled and gender issues and ethics were the most commonly mentioned subjects that were represented in the extracurricular involvement.

Twenty-five per cent of students felt they learned about the EFPO roles through participation in extracurricular activities (Table 3). When asked which roles students considered most relevant to practising physicians, Medical Decision Maker and Communicator received the highest positive responses; 91% and 89% of respondents rated these as "very relevant," respectively (Figure 2). Person and Learner/Scholar also received wide recognition as being "very relevant" by 70% and 66% of

respondents respectively (n=71). The Scientist and Gatekeeper/Resource Manager received the fewest "very relevant" responses, 30% and 34%, respectively (n=71).

**Table 2**
**Did you join any extracurricular activities in order to learn more about a subject that is not taught in the curriculum?**

| Response | % of Respondents (n=48) |
|---|---|
| Yes | 58 |
| No | 42 |

**Table 3**
**Do you feel that your extracurricular activities have furthered your understanding of the physician roles identified by EFPO?**

| Response | % of Respondents (n=65) |
|---|---|
| Yes | 25 |
| No | 69 |
| Don't know | 6 |

Students were assessed about how they felt EFPO should be implemented into the medical school curriculum (Table 4). Asked to select one of four subjective phrases, 4% of students felt that the main focus of the curriculum should be centred around the EFPO roles, while 50% of the respondents thought that the EFPO roles should play an important part in the curriculum (n=71). Seventy percent of students stated that EFPO had limited or no effect on their medical education thus far (Table 5). Furthermore, 86% of students felt that the faculty they had encountered in medical school had not helped them learn about EFPO (Table 6). Fifty-five percent of students felt that it was appropriate to modify the curriculum according to the EFPO roles and 38% felt this was inappropriate (Table 7).

**How relevant do you consider each of the roles identified by EFPO to practising physicians?**

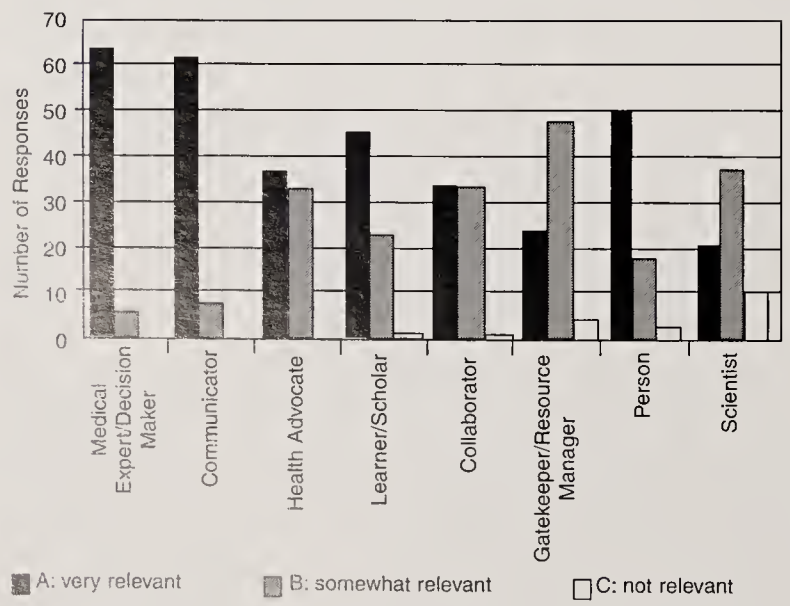



FIGURE 2. *Student Perception of the Relevance of EFPO Physician Roles.*

**Table 4**
**How do you feel that the physician roles identified by EFPO should be implemented into the medical school curriculum?**

| Response | % of Respondents (n=71) |
|---|---|
| They should be the main focus | 4 |
| They should be an important component | 50 |
| They should be a minor component | 30 |
| They should not be there at all | 6 |
| Don't know | 10 |

**Table 5**
**How do you feel EFPO has affected your medical education?**

| Response | % of Respondents (n=71) |
|---|---|
| EFPO has been successful in integrating the needs of the community into medical education | 7 |
| EFPO has had limited success in integrating the needs of the community into medical education | 32 |
| EFPO has had no effect on medical education | 38 |
| Don't know | 23 |

**Table 6**
**Do you feel that most of the clinicians/professors you have encountered in medical school have helped you learn more about EFPO?**

| Response | % of Respondents (n=71) |
|---|---|
| Yes | 13 |
| No | 86 |
| Don't know | 1 |

**Table 7**
**Do you feel it is appropriate to modify your curriculum based on what are the public's expectations of physicians?**

| Response | % of Respondents (n=69) |
|---|---|
| Yes | 55 |
| No | 38 |
| Don't know | 7 |

## Discussion

This study demonstrates the following: 1) consistent with at least one of the eight EFPO roles, medical students at UWO are in fact taking significant measures to supplement their curriculum in areas they feel are inadequately addressed through participation in extracurricular activity, and 2) while medical students at UWO feel that EFPO should influence medical education, strategies to promote the project's mandate have been unsuccessful. Strategies aimed at promoting the EFPO project more efficiently, particularly in the context of extracurricular activity may enhance the overall quality of medical education at UWO.

Students spend an average of approximately 6 hours per week on extracurricular activities that are run by students within the faculty of medicine (Table 1). This can be argued as being the equivalent to one day's worth of lectures. With 15% of respondents spending greater than 10 hours a week and 70% of respondents committed to some extracurricular activity, it is clear that these activities contribute significantly to time allocation within the medical school experience and therefore deserves attention in the field of medical education.

The majority of respondents (58%) felt they supplemented their curriculum and interests by joining activities in order to learn about subjects that were not adequately addressed (Table 2). We propose that students are taking the initiative to educate themselves on issues of personal interest that also concern community groups in a medical context. The clinical scenarios offered in the curriculum to teach psychosocial issues and ethical decision making are being further explored by student initiatives such as gay/lesbian/bisexual forums and creative bioethics discussions outside of class time.

Kuntz (1997) argues that physician-lecturers utilize more inclusive language in lectures because medical students can be impressionable to socially exclusive ideas (e.g. the average 70 kg male).[3] As medical school curricula advances toward independent, problem and case-based learning, students will be expected to take more responsibility for their education; this includes developing tolerant attitudes. It is apparent that students are taking responsibility for developing their own values that will ultimately be employed in their practices.

A student's view of the expectations of physicians as identified by the public is important in determining the effectiveness of implementing EFPO at Western and the attitudes students will have toward patients and community needs. By assessing the relevance of the physician roles, students revealed their general attitudes toward the EFPO project. The relevance of the Medical Expert/Decision Maker, as identified by the response, was expected since this has traditionally been the fundamental role of the physician: to identify and treat disease. The positive response to the Communicator role may be reflective of Western's new admission policies, which require high scores for the Verbal Reasoning and Writing Sample portions of the MCAT and have strong emphasis on the interview, thereby stressing communication skills.

Students presented mixed impressions of the Health Advocate role. The lack of relevance placed on this role is suggestive of a principal often neglected in medical school curricula. As Gunderman (1995) argues, medical school education often fails to address the determinants of healthy living and neglects to instruct students on the factors of an individual's health status beyond medical care.[4] Medical texts, lectures and course notes are organized around the pathological basis of the disease and begin with the assumption that the patient is sick. They look more at diagnosis, pathophysiology and treatment than aspects of disease prevention and health promotion. Clinical instruction and recommended readings have assisted in the instruction of health promotion, however students' responses may indicate a lack of efficacy in the teaching. Students may feel uncomfortable in the role of Health Advocate and may be unaware of the impact physicians can have on disease prevention. Additionally, the meaning of the Health Advocate role may not have been apparent to many students. The term Advocate does not overly suggest to students the role the physician should play in affecting public policy or preventing disease through the counseling of patients.

The Collaborator role also received mixed responses. In daily practice, clinicians are constantly working as members of an interdisciplinary team administering care. It was expected that more students would have responded with a "very relevant" response. This may also be indicative of a lack of understanding of what the role really means. Interestingly, the first theme of the Medicine 2000 Mission Statement incorporated collaborator and health advocate as follows: "As health care advocates we will improve the quality of life through partnership with parents, colleagues and the community."[5] In fact, the goal of the mission statement was to identify as a class what we felt we needed to achieve to serve the public best.

The overwhelming response to the Learner/Scholar role reinforces the commitment to life-long learning and self-directed instruction that has been embraced by most students. These themes are reinforced in problem-based learning and are imperative in view of decreased lecture hours and ongoing advances in medical science.

The negative response given to the role of Gatekeeper/Resource Manager/Steward demonstrates that students do not feel adequately informed to fulfil these roles or have not been shown how the practising physician interacts with social networks and resource managers. There may even be a disagreement that doctors should actually play this role. However, the political understanding that is promoted in hospitals is an intimate communication between physicians and community services in health care management to save health care dollars and practice preventative medicine. According to McWhinney, "the physician is only one of many resources within the community for helping people to deal with their interrelated health and social problems."[6]

In assessing the implementation of EFPO's objective to make medical education more responsive to public needs, 80% of the students felt it should be part of the curriculum in some capacity (Table 4), but 38% felt that EFPO had no effect on their curriculum thus far (Table 5). This may be attributed to a general ignorance of the goals of EFPO. Eighty percent of students felt faculty was unsuccessful in promoting EFPO (Table 6). However, although it is important to clarify the goals of EFPO as an organization, perhaps it is more critical for faculty to focus on educating students about public expectations.

As new directions are taken to modify medical education to reflect the changing needs of society, the entire medical school experience must be explored for educational value. The model we propose for this links the efforts of EFPO with the student initiatives to address what students are taught in the medical curriculum and what they will need to know as physicians. Therefore, understanding students' knowledge of the mandate of the EFPO project can assist the coordinator at the London site in determining strategies for successful promotion of community oriented medical practice.

It is clear that further research in this newly evolving area of medical education is required at all five medical schools in Ontario. With differing demographics and interests, students are pursuing their education in a proactive manner that may be fulfilling many of the roles identified by the EFPO working groups. The role of extracurricular activities in the maturation of medical students into young physicians should be recognized and utilized as a resource in curriculum development. Ultimately, steps toward a collaborative effort between EFPO and students that examines the role of extracurricular activities in medical education may address some of the public's expectations of future physicians.

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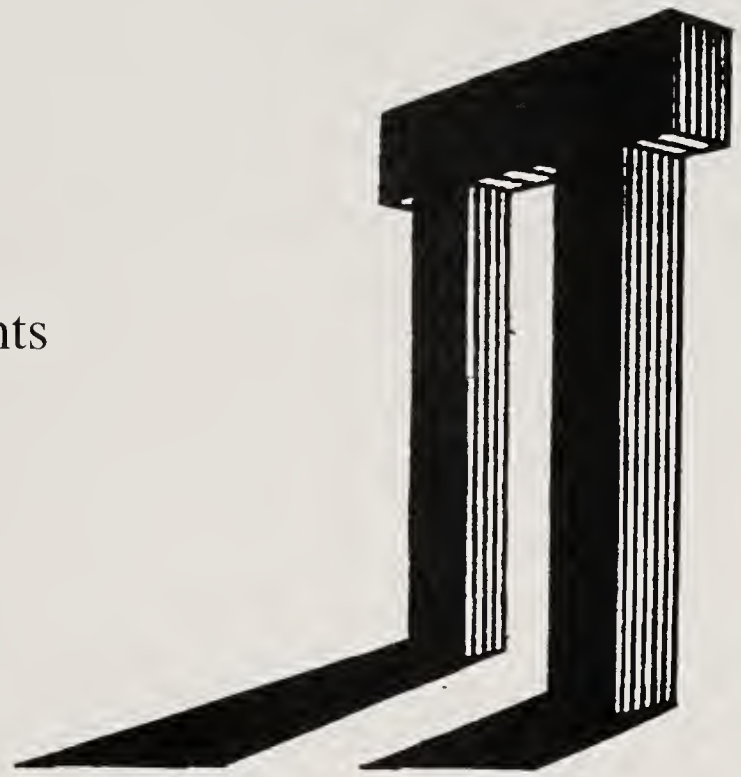

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# Interleukin-6: New Evidence for a Role in Neuronal Regeneration Following Peripheral Nerve Injury

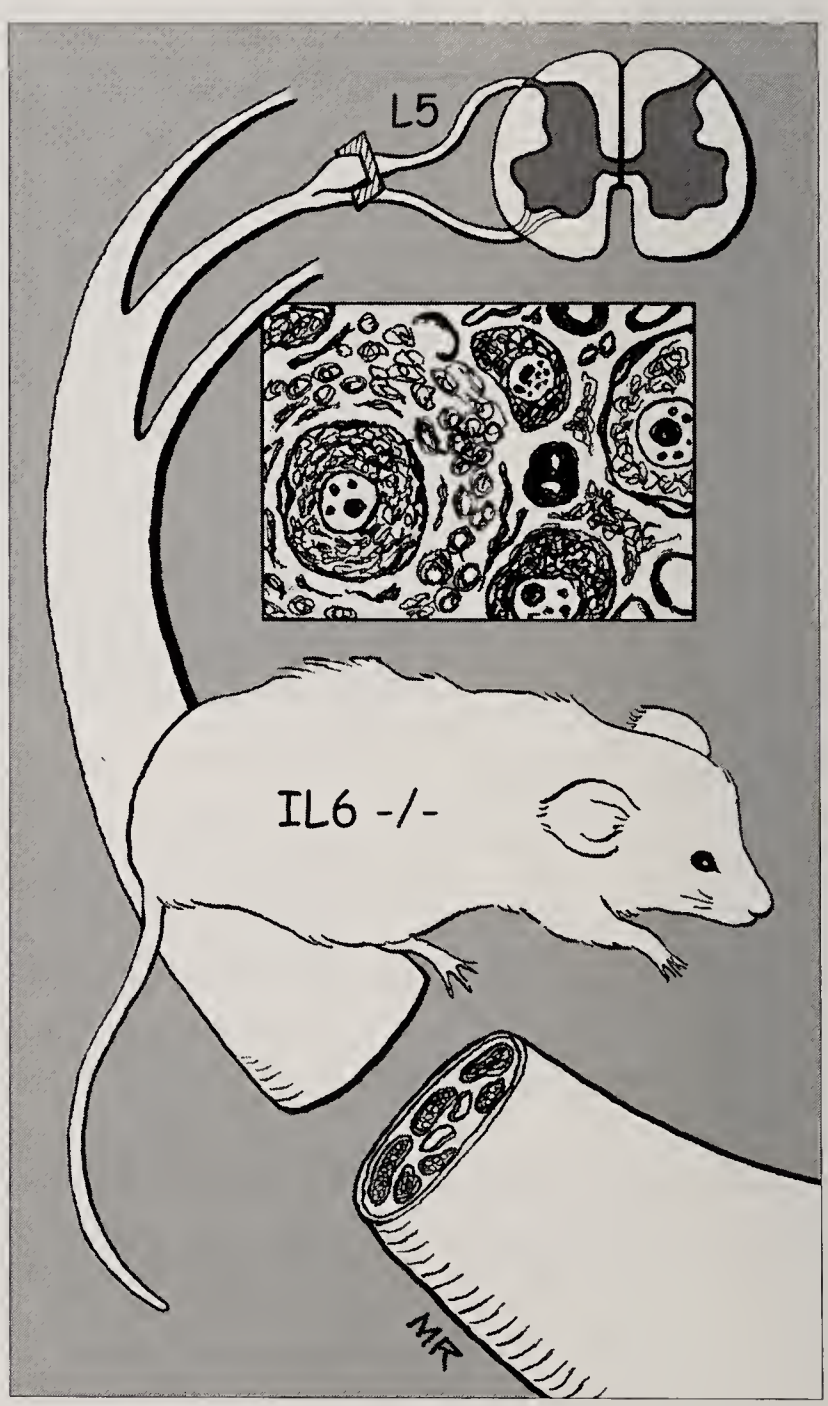
Robert S. Johnston, BSc. (9T9), Patricia G. Murphy,* Ph.D and
Peter M. Richardson,* MD, FRCS

**Abstract**

Interleukin-6 is a cytokine expressed in many tissues in response to trauma, including various components of the nervous system. It has been shown to be both trophic and protective to neurons *in vitro,* and is induced in several cell lines in the mouse nervous system *in vivo* after peripheral nerve ligation. Based on these two findings, it is hypothesized that interleukin-6 helps prevent neuronal death following traumatic nerve injury. A line of mice lacking the interleukin-6 gene provides a useful model for examining this role of interleukin-6. Early findings indicate that mice lacking the interleukin-6 gene show greater loss of neurons in lumbar dorsal root ganglia than do normal mice after sciatic nerve transection.

## Introduction

Interleukin-6 (IL6) is a pleiotropic cytokine with both pro- and anti-inflammatory effects. As a reflection of the marked pleiotropy of this molecule, IL6 has been referred to by at least ten different names, including B-cell stimulating factor 2, Interferon B2, and hepatocyte stimulating factor, depending on the context in which its actions were described. IL6 is perhaps best known for its abilities to stimulate the full range of hepatic acute phase proteins in response to trauma or infection[1] and to induce differentiation among hematopoietic cell lines.[2] It has been known for some time that IL6 is produced throughout the nervous system, but its functions therein have not yet been firmly established. Recent evidence has done much to help establish the role of IL6 in response to nerve injury; studies performed *in vitro* and *in vivo* indicate that IL6 has a protective effect on neurons following injury and acts to promote neuronal regeneration.




Myra Rudakewich

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## IL6 Production

IL6 production has been demonstrated in a seemingly endless variety of cells, including normal human cells (e.g. macrophages,[3] T-cells,[2] fibroblasts,[4] endothelial cells,[5] keratinocytes,[6] mast cells[7,8]), cultured cell lines (e.g. HTLV-1-transformed T cell lines, monocyte lines U937 and P388D1, MG63 osteosarcoma, A549 lung carcinoma),[9] and human tumour cells (e.g. cardiac myxoma, myeloma, hypernephroma).[9] Quantitatively, it appears that the major source of IL6 in humans is accessory cells, although lymphocytes also produce it in large amounts.[10] Significant amounts of IL6 were found to be produced in the folliculostellate cells of the anterior pituitary,[11] which led to the hypothesis that IL6 is an important regulator of hormone production.[12]

IL6 expression has also been demonstrated throughout the rat nervous system, namely in microvessel endothelial cells, astrocytes, microglia, Schwann cells, and most recently neurons.[5,13-16] Northern blot analysis has shown mRNA for the IL6 receptor (IL6R) in the rat dentate gyrus, habenulae, dorsomedial and ventromedial nuclei of the hypothalamus, internal capsule, optic tract, piriform cortex, and other structures.[17]

## IL6 and the IL6 Receptor

Given that the post-receptor events of IL6 vary depending on the target cell type and that the cascade of events is subject to modification by other inflammatory mediators, the signalling pathway of IL6 is poorly characterized; however, recent studies have done much to elucidate this pathway.

The receptor complex of IL6 has 2 parts: a membrane-bound, low-affinity ligand-binding domain IL6R and a homodimer consisting of the membrane-bound signal-transducing molecule gp130. When IL6 binds to the IL6R with low affinity, the complex associates with the gp130 homodimer. The gp130 molecules dimerize, and by doing so induce the formation of high-affinity IL6 binding sites and activate the Jak/Tyk family of receptor-associated tyrosine kinases. The result is the tyrosine phosphorylation of many cellular and membrane proteins, including PLCg, p110-PI 3-kinase, PTP1D, ERK1, ERK2, gp130, pp120 src substrate, STAT 91, SHC, NF-IL6, and APRF/STAT3.[18,19]

In addition to pleiotropy, one of the hallmarks of cytokine actions is redundancy. IL6 shares many actions with the related cytokines ciliary neurotrophic factor (CNTF), oncostatin M, and leukemia-inhibiting factor (LIF),[1,20] and the apparent mechanism for this overlap is the signalling pathway common to all of these.[19] Although the receptor complexes for these cytokines show some variation, they all involve the ubiquitously expressed gp130 molecule or a homologue, they all activate the same family of tyrosine kinases, and result in the phosphorylation of the same group of proteins. IL6 maintains some degree of tissue specificity because the expression of the IL6R is limited to IL6-responsive tissues.[18]

There also exists a naturally-occurring soluble form of the IL6R. The purpose of this molecule is unknown but it may prolong the half-life of IL6 in plasma or enhance the sensitivity of cells to IL6. It is known that this soluble form of the receptor allows cells not expressing the membrane-bound form to respond to IL6.[18]

## Activities of IL6 *in vivo*

### A. Acute Phase Response

IL6 has been described in general as a physiological alarm signal, exerting most of its effects in the early stages of the inflammatory response. This is most evident by the role IL6 plays in the Acute Phase Response (APR) following infection or injury, for example. The APR is characterized by fever, leukocytosis, negative nitrogen balance, increased vascular permeability, changes in plasma metal and steroid concentrations, and increased production of hepatic acute phase proteins (APP's). These proteins in humans include fibrinogen, C-reactive protein, complement C3, factor B, haptoglobin, amyloid A, and a number of proteinases.[10] Whereas the cytokines interleukin-1 (IL1) and tumor necrosis factor are capable of inducing a subset of APP's, only IL6 has been shown to induce the entire spectrum.[21] IL6 is also pyrogenic[22] and contributes to the release of adrenocorticotropic hormone,[23,24] thus further contributing to the APR.

### B. B-cell Terminal Differentiation

IL6 has been shown to induce immunoglobulin production in activated B-cells in a dose-dependent fashion without stimulating proliferation.[10,25] Whereas IL6 receptors are expressed in resting T-cells and activated B-cells, they are not found in resting B-cells.[26] This suggests that IL6 plays a role in the later stages of plasma cell immunoglobulin (Ig) production. Indeed, inhibition of Ig production in pokeweed mitogen-stimulated B-cells by an anti-IL6 monoclonal antibody (mAb) was evident even when the anti-IL6 mAb was added 4 days after the start of an 8-day culture.[27] It is now clear that the major role of IL6 in B-cells is to induce the terminal differentiation into Ig-secreting plasma cells.

### C. T-cell Activation and Proliferation

IL6 was first implicated in the activation and proliferation of T-cells when it was discovered that IL6 could replace accessory cells in lectin-induced T-cell proliferation.[28] It was later observed that resting T-cells did not proliferate in response to IL6 unless IL1 was added to the cultures.[29] This synergy between IL6 and IL1 was found to extend to the induction of cytolytic T-cell responses as well.[30] The target cells for IL6 and IL1 action have since been identified as CD8+ cells capable of secreting interleukin-2 (IL2).[31] The consensus model that has emerged has IL6 inducing T-cells to move from G0 to an early G1 phase which is characterized by an enhanced responsiveness to IL2.[10] IL1 is then necessary for the increased production of IL2 by the activated T-cell.[10]

### D. Hematopoiesis

In the same way that IL6 triggers the emergence of dormant T-cells from the G0 phase, IL6 appears to induce the entry of primitive hematopoietic stem cells into the G1 phase.[32] As with T-cells, IL6 does not induce proliferation of stem cells but rather enhances the effects of other hematopoietic factors, namely IL3,[33] GM-CSF,[34] and M-CSF.[35] This effect of IL6 on hematopoeitic stem cells is very similar to that of IL1. It is not

clear whether the two act independently or if one induces the other, but there is some evidence to suggest that IL1 acts indirectly by inducing IL6.[10]

## The Role of IL6 in the Nervous System

A role for IL6 during inflammatory events in the nervous system was first proposed when IL6 was discovered in the cerebrospinal fluid of patients suffering from viral meningitis and encephalitis.[36,37] The actions of IL6 in the CNS are not clear but IL6 has since been implicated in a number of neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and the AIDS dementia complex.[13,38,39]

*In vitro* studies have demonstrated that IL6 acts in the nervous system as both a mediator of inflammation and a neurotrophic factor. The neurotrophic action of IL6 was demonstrated by the elaboration of neurites in cultured pheochromocytoma cells after IL6 was added.[40] As evidence for the role of IL6 as a regulator of inflammation, cultured astrocytes and Schwann cells were shown to secrete IL6 in response to known inflammatory stimuli including neurotropic virus, bacterial lipopolysaccharide, tumor necrosis factor-$\alpha$, interferon-$\gamma$, and IL1a.[15,41,42]

Addition of IL6 enhances the survival of several types of neurons in culture. More importantly, IL6 attenuates the toxic effects of 1-methyl-4-phenylpyridinium (MPP+) and N-methyl-D-aspartate (NMDA) on striatal neurons,[43,44] suggesting that in addition to its trophic effects, IL6 conveys some protection to injured neurons. These effects coincide with those of the related neurotrophic cytokines CNTF and LIF.

Studies conducted *in vivo* have similarly demonstrated an inflammation-regulating role for IL6 following nerve injury. Northern blot analysis of lumbar dorsal root ganglia (DRG) in the rat after sciatic nerve transection has shown upregulation of IL6 mRNA as early as 12 hours post-injury.[15] Similarly, upregulation of IL6 mRNA has been found in the rat facial nucleus beginning 8 hours after facial nerve ligation and peaking at 24 hours.[45] Increased IL6 gene transcription is thus one of the earliest changes to occur in neurons after injury, preceding the upregulation of calcitonin gene-related peptide mRNA in motoneurons (at 16 hours) and glial fibrillary acidic protein in astrocytes (at 24 hours).[45] The cellular source of the upregulated IL6 transcription has been debated, although the absence of infiltrating B cells and macrophages in the facial nucleus rules out these cells. Similarities between macrophages and microglia has led some authors to predict that microglia are the source of IL6 after injury. More recent work using the RT-PCR technique, RNase protection assay, *in-situ* hybridization, and bioactivity assay has demonstrated that the source of increased IL6 production following sciatic nerve injury is not glial cells or infiltrating cells but is in fact a subpopulation of medium- to large-sized neurons within the injured nerve.[16] It was then proposed that IL6 acts by a direct intraneuronal mechanism, initiated perhaps by interruption of retrograde axonal transport, to affect changes in the synthesis of growth- or apoptosis-related factors.[16]

Another model was proposed based on the finding that addition of a circulating monoclonal anti-IL6R antibody reduces the number of surviving neurons in rat lumbar DRG 5 weeks after sciatic transection.[46] This model is similar to that proposed for the effect of CNTF, in which the cytokine is produced by Schwann cells at the site of the lesion, entered into the axon via receptor-mediated endocytosis, and is transported retrogradely to the cell body. However, immunostaining was unable to detect more than marginal upregulation of the IL6R in the injured nerve. Furthermore, the immunostain that detected IL6 in the Schwann cells at the site of the lesion was performed 1 week after injury – well after the peak IL6 upregulation occurs. It is thus not possible to say that the IL6 found in the Schwann cells was indeed synthesized there.

### *The IL6 Knockout Mouse*

The development of a strain of mice homozygous for a null mutation of the IL6 gene (IL6 -/-) provides a useful model to help ascertain the role of IL6 after peripheral nerve injury. Promising new findings indicate that there is increased neuronal loss in lumbar DRG in the IL6 -/- strain two weeks after sciatic transection; however, there is greater variation in the amount of cell death seen in the IL6 -/- as compared to the IL6 +/+ control strain, making these findings difficult to interpret. Any protection conveyed by IL6 is only partial and likely complements the effects of other factors such as CNTF or LIF. It is possible that such overlapping pathways may serve to compensate for the deficiency of IL6 in the IL6 -/- strain to a highly variable extent.

Even if it is shown conclusively that IL6 -/- mice show increased neuronal death following nerve injury, there remains the issue of whether the lack of IL6 is important at the time of injury or during the development of the nervous system. In other words, is IL6 a beneficial component of the inflammatory response to injury or are neurons that grow in the absence of IL6 inherently more sensitive to injury? Much is known regarding the effect of the IL6 null mutation on the hematopoietic and immune systems,[47-49] but defects in the developing nervous system are not yet known. Much work is needed to identify the role of IL6 during development before conclusions can be made from this type of experiment with the IL6 -/- mouse. Elevated concentrations of IL6 in DRG and other tissues during development[16] suggest that IL6 does play a role in growth and differentiation of neurons. However, a few findings support the idea that other pathways provide enough overlap that IL6 is not absolutely necessary for normal development. First, the number and size of neurons observed in the lumbar DRG of the IL6 -/- strain is not different from the IL6 +/+ strain (unpublished observation). Second, the null mutation is inherited in a Mendelian pattern and adult females bear normal litter sizes,[49] implying that IL6 is not needed during embryogenesis and gestation. Third, adults of both the IL6 -/- and IL6 +/+ are equal in weight, implying that the neuroendocrine system is intact (unpublished observation).

Theories on the mechanism whereby IL6 might protect nerves following injury are largely speculative at this time. As mentioned above, IL6 may have an autocrine effect on injured neurons resulting in changes in the regulation of growth-related or apoptosis-related proteins. IL6 may also have a paracrine effect on perinuclear cells with similar results. Another possibility is

that IL6 expression is necessary to induce the infiltration of macrophages into the DRG after peripheral nerve injury – an event known to be beneficial to injured neurons.[50,51] An interesting experiment would be to compare the degree of macrophage infiltration in the DRG of IL6 -/- mice to that seen in IL6 +/+ mice following nerve injury.

## Summary

There is a substantial amount of evidence to suggest that IL6 is one of several cytokines that are useful in promoting the survival and regeneration of peripheral neurons following injury, but this effect has not yet been proven *in vivo*. A strain of mice lacking a functional IL6 gene provides a potential control for the actions of IL6 *in vivo,* but it must first be shown that the nervous system in this strain of mouse is normal in its development. Experiments with this strain will do much to elucidate the physiology of IL6 and likely provide further understanding of the pathophysiology of neuronal death following traumatic events, and during the course of neurodegenerative disease.

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# Approach to Acute Abdominal Pain in Primary Care

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**Abstract**

Abdominal pain represents one of the most common complaints to primary care physicians in the family practice office or the emergency department. It is also one of the most challenging presentations, making it absolutely critical that a variety of important conditions are considered or excluded prior to disposition. Several groups of patients represent a particular diagnostic challenge, including children, women (pregnant and non-pregnant), the elderly, and immunocompromised patients. This article reviews a primary care approach to acute abdominal pain, and explores modifications based on the etiologies found in various patient populations, namely pediatric, geriatric and obstetric/gynecologic.

## Introduction

When patients present with acute abdominal pain the main task of primary care physicians is to discern between a surgical and a non-surgical abdomen. They must identify potential problems requiring prompt intervention. As the patient's first contact with the medical system, they ought to be thoroughly familiar with many different conditions responsible for this presentation. They must also be able to alter the diagnostic approach based on the age and gender of the patient. In this paper, we will outline the approach to abdominal pain for patients presenting to primary care physicians in the office or emergency department. We will discuss how this approach can be individualized for the pediatric, gynecologic, obstetric, geriatric, and the immunocompromised patient.

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Careful review of patients' signs and symptoms helps to identify the seriousness of their complaint. The following is a descriptive list of some of the "red flags" to which one should pay particular attention.

### A. Pain Characteristics

i. Pain is severe enough to awaken patient from sleep
ii. Pain is getting progressively worse.
iii. Pain fits a specific pattern (e.g. periumbilical pain which shifts to the right iliac fossa characteristic of acute appendicitis).
iv. Pain is accompanied by pre-syncope or syncope (e.g. ruptured abdominal aortic aneurysm).
v. Pain precedes vomiting (100% of patients with surgical abdomen vs. 20% with medical abdomen).
vi. Pain is aggravated by breathing or change in body position and movements.
vii. Pain radiates (e.g. biliary colic usually radiates from the right upper quadrant to the back or right shoulder).

Location alone, although important, may not be a reliable indicator of the anatomical site involved. For example, inflammatory bowel disease may present with pain anywhere in the abdomen. However location, taken together with other associated symptoms or signs (e.g. right lower quadrant pain followed by emesis, fever, and leucocytosis in appendicitis) can be very helpful. An epidemiologic prospective study which looked at the relationship between location of abdominal pain and a specific diagnosis, reaffirmed the efficacy of medical history taking and physical exam in identification of abdominal disease. This study showed that 65% of patients with acute appendicitis had right lower quadrant pain on presentation.[1] Another retrospective study demonstrated that over 60% of women presenting to the emergency department with acute suprapubic pain were diagnosed with a gynecologic etiology, while less than 25% were GI-related.[2]

### B. Persistent Vomiting

### C. Altered Bowel Function

Constipation or obstipation may be the presenting complaint in bowel obstruction, while diarrhea is more typical of infectious or inflammatory gastrointestinal conditions.

### D. Altered Behaviour

Changes in appetite, sleep patterns, energy, and mental status may replace pain symptoms, especially in extremes of age.[3]

### E. Medical and Surgical History

The presence of atrial fibrillation should raise the suspicion of an ischemic bowel from superior mesenteric artery occlusion by an embolus. Inflammatory bowel disease or diverticular disease may lead to perforation and abscess formation. Previous abdominal surgery predisposes to bowel obstruction secondary to adhesive disease. Past history of gallstones may be associated with cholecystitis, pancreatitis, biliary obstruction, and gallstone ileus.

### F. Medication History

A medication history is mandatory. Antibiotics may cause abdominal discomfort, while corticosteroids may mask or diminish pain. Drug toxicity (e.g. lithium) can also manifest with GI symptoms. Use of Non-Steroidal Anti-Inflammatory Drugs and/or alcohol increase the risk of gastropathy, peptic ulcer disease, and gastrointestinal bleeding.[3]

### G. Rebound Tenderness, Guarding, and Rigidity

These manifestations are frequently found in surgical abdomens.

### H. Abnormal Bowel Sounds

Bowel sounds are diminished or absent in peritonitis or ileus, and hyperactive high-pitched "rushes" may be heard in bowel obstruction.

### I. Fever

Fever is a common finding in surgical abdomens. Charcot's triad of fever, right upper quadrant pain, and jaundice may be present in ascending cholangitis.

### J. Specific Signs

The iliopsoas, Rovsing, and obturator signs may be positive in acute appendicitis, but may also be present in almost any condition causing peritoneal irritation.

### K. Laboratory Investigations

White cell count elevation (with left shift) is present in infectious or inflammatory states. Amylase is significantly elevated (>3 fold) in acute pancreatitis, but mildly to moderately elevated in many other conditions such as peptic ulcer penetration and mesenteric infarction. Hematuria or pyuria on urinalysis may be found in renal colic or a urinary tract infection. ALP elevation is seen in cholestatic disorders such as common bile duct stones, while a rise in AST and ALT alone is more likely to suggest medical etiology such as hepatitis.[3]

### L. Abnormal Radiologic Findings

Chest x-ray can show diseases above the diaphragm in patients presenting with abdominal pain (e.g. pneumonia). It may also show free air under the diaphragm in viscus perforation. Abdominal films are helpful in specific diagnosis, such as air-fluid levels and intestinal loop distension in bowel obstruction; however, they are positive in less than 15% of cases of appendicitis (i.e. dilated appendix, presence of fecalith, sentinal loop). Therefore, normal abdominal films do not exclude conditions such as appendicitis. Ultrasound is a very useful tool in investigating gallbladder and biliary disease, urolithiasis and identifying a gynecologic etiology. More sophisticated studies, such as barium x-rays or abdominal CT scan, intravenous pyelogram for obstructive uropathy (e.g. renal stones), or angiography for suspected bowel ischemia or ongoing GI bleeding may be helpful in selected cases.

## Pediatrics

Gastrointestinal complaints are a common presentation in the pediatric population. A careful history and physical exam are necessary to determine whether symptoms are due

to primary gastrointestinal or genitourinary illness or systemic disease states producing abdominal complaints. These systemic states range from the common Strep throat and otitis media to the rare sickle cell crisis (vaso-occlusive crisis) in patients with sickle cell anemia.

It is extremely important to recognize specific disease entities that are associated with particular pediatric age groups. For instance, intestinal obstruction in the newborn raises the concern of congenital esophageal atresia, imperforate anus, or pyloric stenosis. In infants and preschoolers, trauma, pneumonia, intussusception, incarcerated hernias, urinary tract infections, intestinal malrotation, and volvulus must be considered.[4] In the older child and adolescent, appendicitis is extremely common and may be difficult to distinguish from gastroenteritis.[5] Gastroesophageal reflux, constipation, and inflammatory bowel disease are also common in children of school age. Less common causes of abdominal pain that should be included in your differential diagnosis include Henoch-Schonlein purpura, infectious mononucleosis, lead poisoning, and diabetic ketoacidosis.

In the adolescent female, mittelschmerz (bleeding around the ovulation site irritating the peritoneum and resulting in intermenstrual pain), ectopic pregnancy, ovarian cysts, and pelvic inflammatory disease are important.[7] Lab data such as complete blood count (and differential), urinalysis, ß-hCG, and imaging modalities like ultrasound and plain films, support the findings of a careful history and physical examination.

Timely diagnosis and surgical consultation is required for all suspected cases of surgical abdomen in this age group as a delay in necessary surgical intervention may be disastrous. A retrospective study analysing admissions of children with acute abdominal pain over a 3-year period showed that over 50% were discharged without surgical intervention; in this group, the most frequent diagnosis (70%) was abdominal pain of unknown etiology. Of those having surgery, 75% had proven appendicitis on histopathology, while the remaining were reported as normal and no other surgical cause was identified. Less than 4% of children having surgery had another surgical cause for their pain, such as Meckel's diverticulitis, adnexal pathology, mesenteric adenitis, and omental torsion.[6]

## Gynecology/Obstetrics

Women in the reproductive years who present with acute abdominal pain provide a distinct diagnostic challenge, as the causes of abdominal pain in this population are variable and numerous. Common gynecologic conditions include ruptured ectopic pregnancy, salpingitis, and hemorrhagic ovarian cyst.[7] Degenerating fibroids and adnexal torsion occur less frequently. Menstrual history is especially valuable, since temporal relationship between pain onset and last period may provide clues with regards to early pregnancy complications. Pelvic exam may exhibit uterine motion tenderness, commonly associated with PID, or adnexal motion tenderness associated with ectopic pregnancy or cystic ovaries.

A good clinical pearl to remember is "All heterosexual women of reproductive age presenting with acute abdominal pain are pregnant until proven otherwise and require a pregnancy test." Female patients whose history suggests acute salpingitis may actually have an ectopic pregnancy. Importantly, pregnancy may coexist with independent pathology, and thus influences management.

Important diagnostic tests in the female population include ß-hCG, vaginal cultures, culdocentesis, and ultrasound. Positive cervical gram-stains and cultures for gonorrhea and chlamydia do not prove pelvic inflammatory disease; positive cultures are often found in the asymptomatic patient. Conversely, many patients with pelvic infections proven by laparoscopy have negative cervical cultures. Nevertheless, cultures should be collected in order to guide subsequent antibiotic therapy, as well as treatment of sexual partners. Culdocentesis is an easily performed diagnostic procedure that can evaluate peritoneal contents. Clear, straw-coloured fluid represents a negative test, indicating no intra-peritoneal bleeding. Cloudy peritoneal fluid containing white cells suggests an inflammatory process. A bloody tap suggests intraperitoneal hemorrhage, such as from ruptured ectopic pregnancy or ovarian cyst. Ultrasound (transvaginal or transabdominal) has become extremely useful in identifying the location and gestational age of early pregnancies, adnexal or uterine masses, and determining presence or absence of pelvic abscess or excessive free fluid in the cul-de-sac.[7]

The diagnosis and management of abdominal pain in pregnant women is made even more complex by both the altered anatomy of the enlarging uterus (distorting normal architecture) and the altered physiology which changes laboratory values (e.g. elevated WBC count). Surgical disorders may be incidental or directly related to the pregnancy. Therefore, diagnostic evaluation requires careful elicitation of symptoms which may mimic normal discomforts of pregnancy. The goal is to manage the case without resorting to diagnostic aids that may involve potential harm to the developing fetus. Pain characteristics may provide the initial diagnostic clue. Generalized abdominal pain may suggest peritonitis secondary to bleeding or leakage of intestinal contents, while midline cramping of the lower abdomen points to a uterine disorder. Suprapubic pain on either side may signify torsion, rupture, or hemorrhage of an ovarian cyst or tumour. The stage and status of pregnancy should also be considered; for instance, periumbilical pain early in gestation may suggest an intestinal disorder, whereas similar pain in the 3rd trimester may be due to placental abruption. Associated symptoms are also helpful in differentiating causes of abdominal pain in this population. Syncope associated with signs of peritoneal irritation usually indicates an acute abdominal emergency with rupture of viscus or hemorrhage. Fever may suggest infection, such as chorioamnionitis, while vaginal bleeding usually points to an intrauterine problem.[7]

Appendicitis, symptomatic gallstone disease, and ovarian masses are frequent extrauterine complications in pregnancy. Below is a brief description of each condition.

### A. Appendicitis

Appendicitis is a common extrauterine complication in pregnancy (1 in 1000 pregnancies). Rupture occurs 2-3 times more often in pregnancy due to delays in diagnosis and operation.[8] Right lower or right upper quadrant pain from upper displacement of the appendix towards the right subcostal area is usually present but may be ascribed to round ligament syndrome or urinary tract infections. Guarding and rebound tenderness are much less demonstrable as pregnancy progresses. Temperature and pulse may be normal, and urinalysis may reveal pyuria and hematuria, due to appendix proximity to the retroperitoneal ureter, making the diagnosis even more difficult. Presence of anorexia, nausea and vomiting, and vaginal and rectal tenderness aid in the diagnosis.

### B. Symptomatic Gallstone Disease

Symptomatic Gallstone Disease is one of the most common conditions in pregnancy (3-4% pregnancies). High levels of circulating progesterone result in increased bile volume and decreased bile emptying, increasing the likelihood of stone formation. Anatomic changes make it difficult to differentiate cholecystitis from appendicitis. One should pay attention to the nature and pattern of pain, which is similar to biliary colic, presence of Murphy's sign, abnormal liver enzymes (20% of cases), and ultrasound findings such as gallstones, thickened gallbladder wall, pericolic fluid collection, or even swelling in the pancreas.[8]

### C. Ovarian Masses

The incidence of complications from ovarian cysts in pregnancy rises during pregnancy. They are found in 0.1% of all pregnancies, and are usually asymptomatic unless rupture or torsion occurs (2% of masses).[8] Benign ovarian cysts are most common, and are usually teratomas.

## Geriatrics

Evaluation of the elderly patient represents a unique challenge due to the high incidence of coexisting illnesses influencing the patient's condition. Additional challenges include insufficient history and clinical findings in acute abdominal conditions, poor reliability of diagnostic procedures, and the variable presentations of diseases which carry significant morbidity and mortality.[9] One must entertain a wide differential and have a low threshold for admission. Often, more extensive evaluation in this patient population is warranted. A retrospective study evaluating the usefulness of temperature and lab screening tests (Hb, WBC, LFTs, lactate) in patients over 65 who presented to the emergency department with acute abdominal pain, demonstrated that these tests do not differentiate surgical from nonsurgical diseases.[10] Physicians must be aware that their clinical impression of surgical illness is of greater importance than laboratory data in the decision to request special studies or surgical consultation in this population.

## The Immunocompromised Patient

Most patients with immune deficiency, whether from HIV, immunosuppressive drugs, bone marrow disturbances or blood dyscrasias, who complain of abdominal pain have gastroenteritis or enterocolitis. However, some may have serious intra-abdominal infections and surgical conditions requiring immediate intervention. Factors that may obscure clinical judgement include a somewhat different set of symptoms, signs, and laboratory findings then in the general population. In addition, patients with impaired immune systems may have etiologic agents and clinical syndromes that differ from patterns of abdominal pain in the general population.[11]

Most HIV-positive patients presenting with acute abdominal pain have a low CD4 count and have had an AIDS-defining illness, although abdominal complaints may occur in all stages of HIV infection. Symptoms commonly found in chronically-ill AIDS patients include nausea and vomiting from anti-retroviral drugs and PCP prophylaxis, and diarrhea which may be infectious or malabsorptive. Fever is a less specific sign and is often due to the HIV viremia. Tenderness is also non-specific, but helpful when accompanied by other peritoneal signs. The rectum should be carefully examined for discharge which may be the result of infectious proctitis, and prostate tenderness from cryptococcal prostatitis. Laboratory evaluation should take into account the chronic nature of the disease. Baseline anemia is common, and low Hct can be seen with AZT therapy. AIDS patients do not typically exhibit elevation in WBC, but neutrophilia may be seen with sepsis. In addition, although transaminitis is quite common, biliary obstruction generally exhibits a significant rise in ALP. In general, choice of imaging techniques and specialized investigations is the same as for patients with an intact immune system.[11]

The etiology of abdominal pain in immunocompromised patients is variable, ranging from neoplasms to a wide variety of opportunistic microorganisms. The following is a brief description of opportunistic infections and neoplasms found in these patients.

### A. Cytomegalovirus Infection

This is the most common cause of surgical abdomens in AIDS patients. The pathophysiologic mechanism appears to be mucosal vasculitis leading to ulceration, bleeding, and perforation. Cytomegalovirus infection has been implicated in hepatobiliary disease, such as cholecystitis, hepatitis, and pancreatitis.

### B. Kaposi's Sarcoma (KS)

Although usually affecting skin, KS in the GI tract has been implicated in appendicitis, obstruction from bowel involvement or retroperitoneal adenopathy, and GI bleeding.

### C. Lymphoma

Close to 15% of AIDS patients with lymphoma have GI involvement, usually manifested as a partial or complete bowel obstruction due to bowel involvement or external compression by enlarged lymph nodes.

### D. Bacterial Infections

*Clostridium difficile* colitis may follow chronic antibiotic or

AZT therapy, and presents with acute onset of crampy pain, fever, and diarrhea.

### E. Mycobacterial Disease

Nonpulmonary TB involving the GI tract or mesentery can cause partial or complete obstruction. More common is GI involvement with atypical mycobacterium, causing a spectrum of disease from hepatitis to infectious diarrhea and bowel obstruction.

### F. Protozoa

*Cryptosporidium* typically inhabits the small bowel and commonly causes malabsorption and profuse diarrhea. *Giardia lamblia* (giardiasis) has similar manifestations. *Entamoeba histolytica* (amebiasis) has a predilection for the large bowel, although complications such as colonic perforation and hepatic abscesses are rare. *Toxoplasma gondii* commonly affects the CNS, and GI involvement is usually concurrent with CNS toxoplasmosis.

### G. Mycoses

*Histoplasmosis capsulatum,* a yeast with predilection for the lungs, may cause disseminated disease occasionally involving the GI tract, especially the omentum and mesentery.[12]

## Conclusions

In summary, four general approaches to acute abdominal pain in primary care are as follows:

1. Primary care physicians need to individualize their approach when evaluating patients presenting with acute abdominal pain. Proficiency in the recognition and interpretation of important clinical symptoms, physical signs, laboratory data, and radiographic findings, will help to differentiate surgical from nonsurgical cases.

2. Specific attention must be paid to differences in presentation of abdominal pain in males and females. In female patients a gynecologic etiology should always be suspected and investigated along with GI etiology. In male patients testicular pathology (e.g. testicular torsion) may present as suprapubic or flank pain.

3. Diseases manifest themselves differently in various age groups. Physicians must adjust their history taking and examination styles and modify their investigative strategy in extremes of age.

4. Uncommon etiologic agents in immunocompromised patients do not necessarily change the presentation of an acute abdomen. However, the symptoms and signs in such patients may be masked by chronic illness. This makes arriving at the correct diagnosis even more difficult and challenging in this population.

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# In the Literature

### Telomeres and Aging: Ending the Controversy?

Normal cultured human cells have a finite lifespan, ultimately entering a non-dividing viable state termed senescence. The entry of cells into senescence is determined by the number of cell divisions, suggesting that proliferation is controlled by a mitotic clock. Over the past decade, the exact molecular mechanisms underlying the aging process have been the subject of much research and controversy. A leading theory is the telomere hypothesis of cellular aging, which posits that cells age as their telomeres (short sequences of DNA at the ends of chromosomes) are progressively shortened with each cell division. An American study has now provided direct evidence for a causal link between telomere shortening and cellular senescence. Researchers found that human cells transfected with the enzyme telomerase had elongated telomeres, divided vigorously and exceeded their normal lifespan by at least 20 doublings. In fact, at the time of publication, all of the telomerase-expressing clones continued to divide rapidly, showing no signs of senescence. The ability to rejuvenate human cells has extraordinary implications for basic and applied medical research. However, the question still remains whether cellular lifespan can be extended *in situ,* and ultimately, whether this is desirable.

*Source: Bodnar et al. (1998). Science 279:349.*

### An Orgasm a Day Keeps the Doctor Away?

A recent epidemiologic study of Welsh men has made a provocative link between sex and death. Researchers conducted a cohort study of 918 men aged 45-59, examining the association between frequency of orgasm and mortality. The results? Mortality risk was 50% lower in men with high orgasmic frequency than in those with low orgasmic frequency, with evidence for a dose-response relationship. Similar results were obtained after adjusting for age and risk factors such as coronary heart disease, social class and smoking, thus supporting the strength of the association. The authors noted that these findings contrast with the view common to many cultures that sexual pleasure comes at the cost of vigour and wellbeing. If these results are validated by others, we may soon see the day when regular sexual activity is promoted by public health officials as part of a balanced lifestyle.

*Source: Smith et al. (1997). BMJ 315:1641.*

### Interleukin-4 Receptor Mutations and Allergies

Atopic (allergic) diseases are very common in North America, affecting up to 40% of the population. Although environmental factors such as exposure to antigens play an important role in the pathogenesis of allergy, there is also a strong genetic predisposition. Central to the allergic response is IgE, which binds allergens and causes the release of inflammatory mediators from basophils and mast cells. Now, American researchers have discovered a mutation in the gene encoding the interleukin-4 receptor that predisposes individuals to atopy. IL-4 is a key cytokine involved in the production of IgE by B cells. Carriers of the receptor mutation were found to have a 9 fold increased risk of suffering from atopy. Analysis of patients' mutated receptors revealed them to be hyperactive, with inappropriately enhanced signal transduction. These findings may eventually lead to more targeted medications for allergic disease.

*Source: Hershey et al. (1998). NEJM 337:1720.*

### Risk Factor for Prostate Cancer Identified

Unlike its more famous cousin, breast cancer, relatively little is known about the etiology and pathogenesis of prostate cancer, the most prevalent cancer diagnosed in men. However, researchers at McGill and Harvard have found that men with high plasma levels of Insulin-like Growth Factor (IGF-1) have

a 4-fold increased risk of developing prostate cancer when compared to men with low IGF-1 levels. In this study, IGF-1 levels were measured in 152 men diagnosed with prostate cancer and 152 healthy controls. Until now, the main risk factors for developing prostate cancer were age, race and family history, but with these new findings, IGF-1 would now appear to be the strongest known risk factor for this common disease.
*Source: Chan et al. (1998). Science 279:563.*

### Quality vs. Quantity of Life

Prevailing wisdom suggests that quality of life is an important aspect of elderly patients' lives. However, a recent study has found otherwise. Hospital patients aged 80 and older and their surrogate decision makers were independently asked whether the patients would prefer living one year in their current state of health, or less time in excellent health. Although only 30% rated their current quality of life as excellent or very good, a surprising 68% said they would prefer to live for 12 months in their current state rather than one month in excellent health. In addition, researchers found that surrogate decision makers were not always aware of patient preferences - patients were willing to trade far less time for a healthy life than their surrogates assumed they would. In light of their findings, the authors urge physicians to assess the health values of patients on an individual basis when contemplating aggressive medical care for the elderly.
*Source: Tsevat et al. (1998). JAMA 279(5).*

### Toronto Team Touts Terrific Test

Research conducted at The Toronto Hospital and the Canadian Red Cross by Dr. David Phipps and Dr. Donald Branch has resulted in the discovery of a new test for the early detection of HIV. Current HIV tests, which measure antibodies produced in response to HIV infection, have a "window period" of six weeks to six months before they can reliably detect HIV infection. However, the new test is based on the Fyn enzyme a protein kinase which is chronically turned on in HIV infected cells in as little as 30 minutes following infection. The authors feel that this new test may eventually replace current testing for HIV.
*Source: Phipps et al. (1997). Blood 90:3603.*

### The Other Side of Fat

A study of participants gathered from the Framingham Heart Study found that intakes of total fat, saturated fat and monounsaturated fat were associated with a reduced risk of ischemic stroke in men. The association persisted even after the data were adjusted for such factors as cigarette smoking and physical activity. These new data emphasize the potential risks of extreme dietary recommendations. It is felt that these insights into risk of stroke are particularly important because specific treatments for acute stroke are few and thus primary prevention is paramount. These data are somewhat surprising in light of the direct association between fat intake and ischemic heart disease. The authors noted that the results of their study must be interpreted with caution and that for the time being clinicians and public health authorities should emphasize other methods for prevention of stroke, such as avoidance of cigarettes, prevention and control of diabetes and hypertension, and treatment of atrial fibrillation.
*Source: Gillman et al. (1997). JAMA 278: 2145.*

### Surprise, Surprise

A January, 1998 study published in the Journal of Studies on Alcohol found that alcohol intake at colleges and universities is directly related to involvement with fraternities and sororities. In particular, fraternity and sorority leaders also lead in their alcohol intake and experience more severe negative consequences than others. The study concluded that leaders are participating in setting norms of heavy drinking and behavioural loss of control. The study attributes this behaviour to students' belief that alcohol is a vehicle for friendship, social activity and sexual opportunity. The study found that nearly two thirds of male fraternity leaders had done something they later regretted while under the influence of alcohol compared to one third of uninvolved males. The authors concluded that prevention programs should focus not only on the drinking behaviour itself but also on the beliefs and norms that are operative among those most influential in the university setting.
*Source: Cashin et al. (1998). J Studies Alcoh 59:63.*

### Angioplasty for Treatment of Myocardial Infarction

A recent meta-analysis found that angioplasty is superior to thrombolytic drug therapy for the treatment of MI. The study found a reduction in mortality, reinfarction and stroke with the use of angioplasty when compared to the thrombolytic agents streptokinase and tissue-type plasmingoen activator (tPA). The strategy of acute angiography and angioplasty has the advantage of a higher initial reperfusion rate than thrombolysis and of defining coronary anatomy and left ventricular function. This, in turn, leads to earlier triage of patients to surgery when necessary and earlier hospital discharge of patients without complications. Despite the promising findings, data evaluating longer-term outcomes, operator experience, and time delay before treatment are needed before primary angioplasty can be universally recommended as the preferred treatment.
*Source: Weaver et al. (1997). JAMA 278:2093.*

### Males' Brains Age Faster than Females'

A February, 1998 study found that brain shrinkage, which is a normal consequence of aging, occurs more rapidly in the brains of males than females. The team of researchers performed quantitative magnetic resonance imaging (MRI) on 330 people between the ages of 66 and 96 living independently in the community. Age-specific changes in brain size were significantly greater in men than in women. The gender related differences were found to be most marked in three regions of the brain that are involved in thinking, planning and memory. It is felt that these findings may help explain the fact that men are more prone to age-related brain disorders such as memory loss and Alzheimer's disease.
*Source: Coffey et al. (1998). Arch Neurol 55:169.*

# Evidence-Based Medicine: A New Science to Reaffirm Old Ideas

Kylen McReelis, BSc. (OTO) and Amish Parikh, BSc. (OTO)

Over the last ten years, virtually every aspect of health care has seen the introduction of Evidence-Based Medicine (EBM) into clinical practice. The explosion in EBM has affected everyone from the research community to the practicing community,[1] influencing the way many physicians incorporate research into medical decision making. One need not go far in the medical literature to stumble upon the words *evidence-based medicine* and unquestionably, they have become the buzz-words of the 1990's and do not show any sign of losing their momentum.

It is now without question that health care practitioners in the coming century, whether they choose to incorporate EBM into daily practice or not, will have to have a knowledge of its relevance for patient care. In the current era of health care cutbacks, decreased research funding, and less time for the average physician to keep abreast of the explosion in relevant biomedical research, EBM has garnered the status of a medical specialty in and of itself.

It seems somewhat ironic that medicine based on evidence is a new philosophy for health care in the 1990's. After all, don't we trust that the medical community has relied on solid scientific proof to guide clinical decision making? Not always, says Dr. David L. Sackett, one of the founding gurus of EBM, who initially began studying EBM at McMaster University in Hamilton, Ontario, and is now director of the Centre for Evidence-Based Medicine at Oxford University, England. He claims that EBM allows physicians to practice medicine that is based on the best available scientific evidence and to not necessarily follow the previous status quo.[2] EBM de-emphasizes the use of intuition and unsystematic clinical experience as sufficient grounds for decision making.[3]

The EBM philosophy is considered to have its roots at McMaster University[4] and the term was officially coined in 1991 by Dr. Gordon Guyatt, a Professor of Medicine and Clinical Epidemiology. Sackett and colleagues state that:

> *EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.*[2]

Individual clinical expertise is much more than clinical proficiency and judgement, and entails an intimate knowledge of a patient's situation, beliefs, and priorities, all of which can be established by taking a patient-centered history. In the search for the best possible screening, diagnostic, or therapeutic intervention, physicians have looked to the randomized control trial (RCT), as the "gold standard" for systematic research. Becoming increasingly popular is the pooling of results from numerous trials, called a meta-analysis, which is now becoming a defined cornerstone of EBM. In fact, the International Cochrane Collaboration is developing meta-analyses of RCT's in all areas of medicine. This collaborative enterprise of health care providers, consumers and scientists has set out to prepare, maintain and disseminate systematic and up-to-date reviews of all relevant RCT's to allow physicians to incorporate EBM into daily practice.[5] Some have described its impact as rivaling the Human Genome Project in its importance to the future of medicine.[3]

From this theoretical basis of EBM, the practical question then becomes how does a clinician, resident or medical student harness the powers of EBM and apply them to patients under their care? Successful EBM can be broken down into five essential steps:[6]

1. Construct a good question as it relates to the patient's specific needs, whether these relate to diagnosis, treatment or prevention. For example, the question "how should men be screened for prostate cancer?" is vague and lacks a specific focus. A better question would be: "Which men should be screened for prostate cancer with PSA - all men above the age of 40, all men with urinary symptoms regardless of age, or all men with symptoms above the age of 40?"

2. Carry out an efficient, thoughtful search for evidence. One can start with MEDLINE, searching under key subject headings.

3. Choose the best and most relevant resources from the search. If possible, try to find a recent RCT that addresses your question.

4. Critically appraise the evidence presented. A useful approach to learning these skills can be found in the series titled the "Users' Guide to the Medical Literature" published in JAMA.[7]

5. Amalgamate the external evidence gained in steps 1 to 4 with clinical expertise to create a mutually acceptable plan with the patient.

When used effectively EBM proponents believe that the conclusions reached will provide patients with more powerful, more accurate, and more efficacious medical care.

However, EBM is not without its critics. It has been labeled as "cookbook medicine"[2] that may be leading us on the road to a future where medical care is determined and delivered by a set of statistical algorithms and a *P*-value. Critics fear a potential disregard for physician and patient individuality, preference and autonomy in decision making. Nevertheless, it seems that EBM is here to stay as shown by its permeation into all facets of health care. It has received increasing attention in the medical literature[8] as shown by entire journals[9] devoted to the topic, the rise of dedicated web sites, and its increasing integration into contemporary undergraduate and postgraduate medical education.[10]

Here in Toronto, residents are receiving exposure to EBM through a variety of structured seminars and courses. According to Allan Detsky, Physician-in-Chief at Mount Sinai Hospital, residents in the Internal Medicine programme receive exposure through a course designed to enhance their ability to critically appraise the evidence for clinical practices that they employ each day on the ward. When asked about how EBM will influence medicine in the coming decade, he said "the volume of literature based on evidence will no doubt continue to increase. However, the major obstacle to EBM being used to its full extent is that technology as of yet, can not provide this information in a quick and meaningful way to the average physician."

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# On the Health Benefits of Alcohol

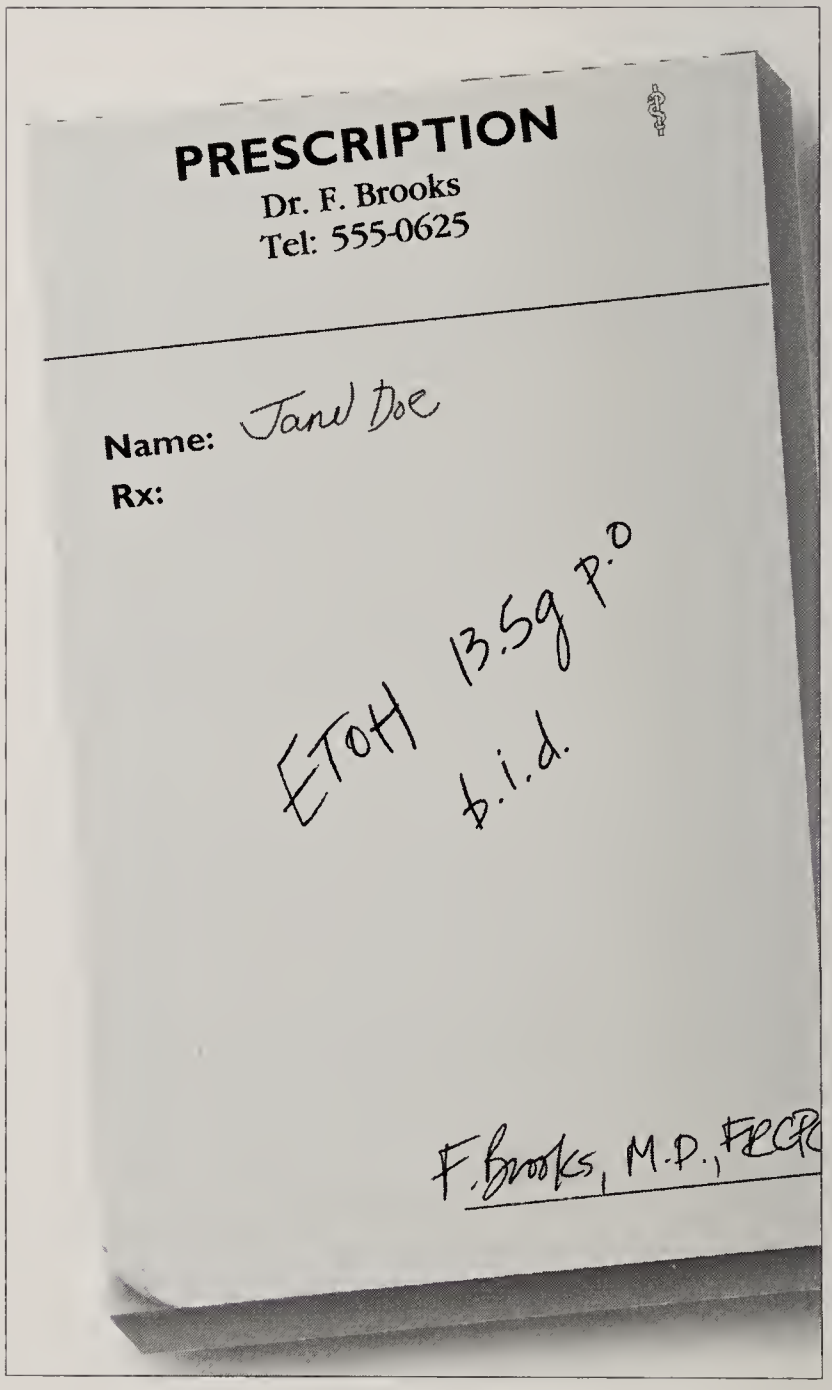
Eyal Cohen, BSc. (0T0)

Every medical trainee can easily recite the myriad of medical complications that result from alcohol, ranging from the all-too-common horrors of drunk driving to even the rarest of sequelae such as Korsakoff's syndrome. Similarly, we are well trained in rattling off the CAGE questionnaire to our OSCE examiners whenever we see a patient who admits to having a drink or two.

In recent years, a compelling and scientifically rigorous mountain of data has demonstrated that moderate alcohol intake protects against the number one killer in North America, coronary heart disease (CHD). In fact, the accumulated evidence seems to point out that the reduction in cardiovascular mortality is of the order of 20-80%, which would make moderate drinking more beneficial than any other intervention in cardiology.[1] Although the exact mechanism of the cardioprotective effects of alcohol has not yet been delineated, it seems to stem from several factors such as elevating HDL-cholesterol, reducing the aggregation of platelets in the bloodstream and increasing the plasma concentration of endogenous tissue plasminogen activator (t-PA).[2]

Unfortunately, it seems that at higher doses, alcohol is detrimental to the cardiovascular system and has been associated with a number of problems such as cardiomyopathy, hypertension, hemorrhagic stroke and arrhythmias.[3] Furthermore, there are no health benefits if the moderate consumption of alcohol is manifested as episodes of binge drinking.

It is clear that alcohol can be both a medical and social menace when taken in excess, but may also act as an enormously beneficial prophylactic agent against heart attacks when taken in moderation. Armed with this information, what do we as future physicians tell our patients? Dr. David Goldberg in the Department of Clinical




Jennifer Bosy

Biochemistry at the University of Toronto recommends the consumption of up to two glasses of any alcoholic beverage per day to both men and women, preferably with meals. An average drink is defined by its alcohol content as 13.6 grams *(Canada),* 12 grams *(USA)* and 8 grams *(UK).* In Canada, maximum guidelines to minimize acute consequences (e.g. traffic accidents) have been set at 27.3 g/day. Dr. Goldberg believes that these limits may be too stringent for certain people, and that depending upon body weight and other factors, men may consume at least four drinks in any one day as long as they are adequately spaced and that they represent an occasional rather than a regular intake. Some believe that of all forms of alcohol, red wine is the most cardioprotective. Evidence favoring this view was presented by Renaud and De Lorgeril (1992) in a paper that first described the "French Paradox."[4] Their data showed that the mortality rate from coronary heart disease is particularly low in France, a country with a high fat intake, heavy use of tobacco and a sedentary lifestyle.[4] However, more recent epidemiologic data in many other populations have failed to confirm the relationship.[5] Patients should also be warned about binge drinking, which Dr. Goldberg defines as up to four drinks or more taken consecutively over a brief period with minimal food intake. For occasional drinkers, Dr. Goldberg recommends an increased consumption of alcohol up to the levels previously defined, but he opposes the idea that abstainers should be encouraged to take up drinking. People who have abstained from drinking throughout their lives may have done so for a variety of personal, cultural, religious or medical reasons and therefore each case must be treated individually.

This type of information is a tough sell on many people in North America, where current recommendations about moderate drinking and health are much more conservative than in Europe.[6] Powered by a strong temperance movement, alcohol is still viewed as an illicit substance that is tightly regulated and heavily taxed. Interestingly, unlike cigarettes, alcohol distribution is monopolized by a single bureaucratic agency in our province. Until very recently, you could buy cigarettes at any time of the day at any corner store, but you could not buy a bottle of wine at an LCBO on a Sunday. Furthermore, in Ontario, a person can own an implicitly lethal weapon at age 16 (otherwise known as a car), can apply for a permit to own an explicitly lethal weapon at age 16 (otherwise known as a gun), but cannot legally drink an alcoholic beverage until age 19. In high schools, alcohol education is primarily restricted to discussions about alcohol abuse which is conveniently clumped with drug abuse. The only information that the public receives on any positive effects of alcohol comes from the lay press and from their physicians. Dr. Goldberg stresses that the proper forum for the education of the public on the possible beneficial effects of moderate alcohol intake should come from public health officials and the school system, rather than the medical profession. He states that "teaching safe alcohol consumption is as important as teaching safe sex," especially considering that the cardioprotective effects of alcohol are probably cumulative over time and hence lifelong prophylaxis is most beneficial.

Like many drugs, alcohol has side effects, contraindications, interactions, and the potential for overdose. Without a doubt it is a dangerous drug when used irresponsibly. Even when consumed in moderation, alcohol can lead to problems such as an increased motor vehicle accident risk.[6] Labels should be placed on bottles outlining standard serving information (something which we find on every bag of potato chips or pop but not on alcoholic beverages), so that people will know that a bottle of beer has the same amount of alcohol as a shot of distilled spirits. We must be able to identify patients who have the potential to become substance abusers, and to the rest of our patients, we must continue to stress the dangers of alcohol abuse. However, as future physicians, we have a duty to inform occasional drinkers about the beneficial effects of alcohol. There is no evidence that adults who don't abuse alcohol will begin to abuse it after they learn about the positive effects of drinking alcohol in moderation. Is it not more likely that we will fulfill our professional mission by helping to promote our patients' lifelong health?


## Acknowledgements

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# Science and Sensationalism: Popular Press Coverage of Antibiotic Resistance

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## Introduction

The recognition of antibiotic-resistant bacteria as a serious public health threat has resulted in increased popular press coverage of resistance-related issues. Many health care groups have welcomed this media response, deeming it essential for improving the current alarming lack of public awareness about the subject. A 1997 Gallup survey revealed that 83% of Canadians are unaware of the definition and consequences of antibiotic resistance.[1] Certainly the potential of the mass media to raise public education is undeniable, and it is quite likely that "the media now functions as the primary connection between science and society on health issues."[2] However, what is rarely considered is the possibility that current methods of press coverage may *not* be fulfilling this potentially beneficial role. The purpose of this paper is to undertake a critical analysis of popular press coverage of antibiotic resistance. More specifically, it aims to establish that rather than concerning itself with fulfilling its role as a source of useful public health information, current press coverage tends to produce sensationalistic stories which maximize readership and sales.

## Sensationalism

The claim that popular press coverage of antibiotic resistance has tended toward sensationalism is supported by previous studies of the relationship between media and science. In 1967, Krieghbaum's *Science and the Mass Media* noted the media's exploitation of "scientific inquiry as a source of startling narratives."[3] Press journalists themselves have admitted to this tendency. Former *New York Times, Washington Post,* and *International Herald Tribune* reporter Stephen Klaidman concedes that "journalistic biases toward a good story, toward balance, and toward conflict...may override the careful reporting of health risks."[4] Clearly then, the concern that such bias may exist in popular press coverage of antibiotic resistance has a solid basis in science-media studies.

Glynn and Tims (1982) provide a useful framework for the analysis of sensationalism in press coverage of science issues by proposing a set of criteria which collectively define "sensationalism."[5] These criteria are: 1) obvious overstatement of fact; 2) exceptional emphasis on unique aspects of the situation; 3) association of the subject matter with an irrelevant issue. This framework provides an effective means of systematically analyzing the press coverage of antibiotic resistance issues.

### A. Obvious Overstatement of Fact: Fear-Arousing Headlines

An examination of antibiotic resistance articles in the popular press exposes a disturbing tendency to overstate concerns. In particular, concerns of increased incidence of multi-drug resistant isolates in hospitals are exploited to convey the notion of serious threat to the general community. This exaggeration of facts is most clearly evident in the headlines of stories; phrases such as the *Toronto Star's* "A Looming Antibiotic 'Apocalypse'" and *Time's* "Revenge of the Killer Microbes" convey an exaggerated sense of urgency to the current situation.[6,7] Similarly, *Maclean's* "Outbreak" cover is accompanied by a graphic displaying a scientist who is garbed in protective gear for his mouth, hands and head.[8] The scientist is holding a test tube surrounded by a menacing fluorescent glow, almost implying

a radioactive nature to the "deadly" resistant bacteria. According to these headlines, resistant bacteria apparently threaten not only severely ill hospital patients, but healthy individuals in the community as well.

A closer examination of Leslie Papp's July 24, 1995 *Toronto Star* article further supports this claim of fear-arousing overstatements. Beside the subheading "it's possible to return to the death rates common before the use of penicillin" is a graphic depicting a skeleton holding a syringe.[6] Like the story headlines, this obvious association of antibiotic resistance with mass death distorts the current state of antibiotic resistance in which resistant bacteria pose significant threats to immunocompromised patients who have undergone chronic treatment with antibiotics. Papp further plays upon this exaggerated urgency of an exhausted antibiotic arsenal in the body of the article, where it is written that in an attempt to discover new antibiotics, desperate scientists "...in the jungles of Zaire are trapping and testing examples of every creature that walks, flies, or slithers through the forest..."[6] Importantly, Papp fails to mention that the vast majority of bacterial infections remains treatable with current antibiotics.

### B. Exceptional Emphasis on Unique Aspects of the Situation: Superbugs

A broad survey of diverse publications reveals an overwhelming focus on one particular aspect of antibiotic resistance: the emergence of the "superbugs" vancomycin resistant *E. coli* (VRE) and methicillin resistant *S. aureus* (MRSA) in hospital settings. Between 1995 and 1996, superbugs were the focus of articles in *Maclean's, The Globe and Mail,* the *Economist,* and *Saturday Night.*[8-11] In many ways, this attention is warranted, since these resistant bacteria represent the most severe and dangerous cases of antibiotic resistant bacteria. However, the articles consistently fail to specify the particular instances in which these resistant bacteria pose legitimate health threats. Instead, nosocomial infections are presented as dangerous to the community, and deaths of chronically ill patients are interpreted as first indications of an inevitable spread to healthy individuals. This failure to contextualize the case-specific threats of MRSA and VRE may thus be interpreted as irresponsible and sensationalistic.

An article by *Wall Street Journal's* Elyse Tanouye published in the Globe and Mail on July 23, 1996 typifies this myopic emphasis on multi-resistant bacteria.[12] The article begins with a frightening account of an elderly woman isolated in a hospital because she harbours a bacteria "untreatable by any antibiotic," which is presumably VRE. Instead of noting that the patient's situation is a special case – that she is severely immunocompromised and likely to have been hospitalized for a long time – Tanouye presents this distinct situation as plausible for many. Tanouye writes that the woman is among "the first wave of casualties," thereby implying that the next unavoidable wave will strike the community.[12] Nowhere in the article does Tanouye make the important distinction between nosocomial and community infections. Instead, the specific case is presented as a general threat to public health.

### C. Association of the Subject with Irrelevant Material: Non-resistant Bacterial Infections and Viral Diseases

The association of antibiotic resistance-related issues with irrelevant material is perhaps the most harmful sensationalistic aspect of media coverage because it serves to further confuse a lay public already intimidated by science. These articles can be classified into two varieties: 1) those which fail to distinguish between non-resistant bacterial infections and those resulting from resistant bacteria, and 2) articles which fail to distinguish between bacterial and viral diseases.

The most prominent examples of the first variety involve making a false connection between antibiotic resistant bacteria and necrotizing fasciitis (more commonly referred to as flesh-eating disease). Group A *Streptococcus,* which causes necrotizing fasciitis, in fact bears little relevance to infections caused by resistant bacteria. Drug-resistant Group A *Streptococcus* has not been detected in Canada, and only a few isolates have been reported in the U.S. The disease can thus be effectively treated with a combination of antibiotics and surgical debridement. Despite these facts, Mark Nichols' cover story of the September 9, 1996 edition of *Maclean's* explicitly makes this incorrect connection between Group A *Streptococcus* and resistant bacteria.[8] Group A *Streptococcus* is included in a list of "drug-resistant bacteria," or "renegade bugs" along with MRSA and VRE. Furthermore, because notable figures, such as Muppet creator Jim Henson and Quebec Premier Lucien Bouchard, were afflicted with necrotizing fasciitis, the mistaken perception arises in the public that antibiotic resistance has caused serious illness and even death to previously healthy people among the general populace.

Articles which link antibiotic resistance with viral diseases perpetuate and reinforce the widely held, erroneous belief that antibiotics are efficacious against viruses such as the common cold. In fact, Gallup research indicates that 49% of Canadians expressed this misguided belief.[1] An Economist editorial from May 20, 1995 serves as an excellent example of this errant connection.[10] After a gloomy introduction which discusses the "terrifying" Ebola virus, the focus of the article subtly shifts to resistance in *Staphylococcus* bacteria via an intermediary discussion of the ambiguous term "germs"; no distinction is made between viral and bacterial "germs." The remainder of the editorial then solely addresses the issue of antibiotic resistance. Consequently, the article unmistakably and misleadingly connects antibiotic resistance with the completely irrelevant issue of the Ebola virus. Articles such as these can

only result in increased ignorance and confusion in the general public.

## Conclusion

### An Alternative Approach to Press Coverage

The above examples have shown how the current sensationalistic approach of the popular press has hampered its potentially positive role as a reliable source of public health information. A shift from the present emphasis on sensationalism to a more balanced reporting of antibiotic resistance issues would seem to be the simple solution. Yet this proposal for more responsible press coverage is also problematic. Dornan convincingly argues:

> "...the issue becomes how, in practice, to produce a science writing that, while true to science, is nonetheless sufficiently arresting to capture widespread public attention. That is, even if the press dramatically increased the quantity and quality of its science coverage, what would guarantee that the laity would respond?"[13]

This concern of maintaining public interest in the absence of sensationalism is a legitimate worry and must be considered in any reforms of current strategies.

A November 20, 1992 *Globe and Mail* article by medical reporter Paul Taylor provides a potential avenue for new directions.[14] Sensationalistic references to fears of mass death are refreshingly absent. Instead, Taylor provides accurate and useful information tracing the development and emergence of antibiotic resistance. He further distinguishes between community and hospital threats as well as between bacterial and viral diseases. Concerns that this unsensational article would lose reader interest are somewhat alleviated by a vivid, yet not misleading, illustration depicting a muscular bacteria smashing a pill bottle presumably containing antibiotics. In addition, Taylor mentions the enormous health care costs arising from the need to use newer antibiotics, a startling economic statistic which would capture the interest of many readers.

The above example illustrates an approach which is far more responsible than the sensationalism which dominates much of the current press coverage of antibiotic resistance. Admittedly, achieving a balance between newsworthy and responsible reporting is often a precarious endeavour. It is this alternative approach, which the print news medium must consider adopting, if it sincerely desires to become a positive contributor in the area of combating antibiotic resistance.

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# Medical Education from an Anatomical Perspective

Brian Rotenberg, BSc. (OTO)

There is a certain consistency to the process of learning medicine. Every new concept or method introduced has its foundation in previously learned material; new information is continually being built upon key fundamentals. What then is the basic building block that underlies medical students' knowledge, irrespective of the medical discipline in question? The answer generally lies in the study of anatomy, which forms the core of most diagnostic reasoning processes. A solid understanding and use of anatomy is the root of a medical student's knowledge and skills. Other medical learning can grow and inter-relate from that foundation, with an emergent goal of possessing the attributes of a complete doctor.

The traits and talents which comprise a complete medical educator *also* have an anatomical basis, albeit different from that of the study of medicine. The essential anatomical characteristics of such a person are the sum of those skills and qualities which set him or her above and apart from other educators. It is the Anatomically Correct Educator (ACE) who can expect to achieve the best learning from his or her students. Possession of that special educational anatomy, and the ability to apply it to the teaching process, is what makes the complete teacher the pick of the crop.

When examining the anatomy of the ACE, the first tissue systems one observes are, just as in the human body, those of the senses. The eyes, ears and skin are marvelous structures, performing in concert the detailed functions of seeing, hearing and feeling the outside environment. The senses of the ACE must be equally perceptive. ACEs are able to see the body language of their learners, and to respond properly. They are *listeners* as well as speakers, able to pick out both the obvious meanings of their learners' comments as well as hidden meanings often obscured by the words. An essential component of good teaching (and consequently better learning) is the ability of the educator to perceive the learner's needs and respond appropriately and effectively.

ACEs sense the importance of verbalizing their thinking processes as they themselves problem solve; this highly distinguishing feature of the ACE's sensory system seems so unassuming that its beneficial effects can be easily overlooked. Most medical professionals, be they staff or residents, might silently look over a sick patient, pause for a few moments, then pronounce such an obscure diagnosis as multiple enchondromatosis with associated visceral hemiangiomas, all without saying a word. This makes sense from his or her point of view, but what could a student possibly learn from such an encounter? The ACE will, on the other hand, examine the patient and *verbalize aloud* his or her thought processes during diagnostic deduction, clearly enhancing the student's potential to learn. Verbalizing is not an easy task, but educators who are able to do so will benefit their students immensely.

Use of the sensory system is not an inherent trait in every educator. Some will forge ahead, unaware that their learners are having difficulty comprehending, or are becoming frustrated. The ACEs, however, are constantly cued into their students' needs and are thus able to sense problems and respond accordingly. Students are acutely aware of which teachers have their sensory anatomy intact, and equally aware of those who do not.

The anatomy of the musculoskeletal system provides a strong yet flexible framework of support for the body. It allows the individual to encompass an extensive range of motion while maintaining stability. As well, with its links to the body's neurological reflex systems and brain, it is able to maintain coordination and a sense of proprioception. The ACE possesses educational anatomical attributes analogous to these.

Through a range of training, be it formal or informal, an ACE develops a framework of skills which manifest themselves depending on the situation. Mannerisms including those of the expert, authority, role model and facilitator, are adopted to support and augment the teaching role.[1] Many teachers can be placed into one, or even a few, of those categories. The ACE, however, can encompass the entire range of the support framework while also intuitively knowing how and when to change from one mannerism to another (one of the quintessential qualities of the complete teacher). This ability to shift roles strongly facilitates the ACE's teaching, for he or she will also have a strong proprioceptive sense of which role they are in at any given time, and *why*. Mastery of the educational musculoskeletal anatomy is a vital and fundamental characteristic of the ACE, who must possess the 'educational body types' of both the bulky power weight lifter and that of the lithe and endurable marathon runner.

The physiological circulatory system is driven by the heart, and through its action sustenance and functionality is provided to the body's tissues. However, in an educational sense, the cardiac anatomy must be construed more in its folk meaning, as being the proverbial seat of *empathy* — an essential quality in the whole and perfect teacher.

The heart-centered empathy of an ACE is manifested in two distinct ways. The first is that complete teachers will be able to demonstrate true interest in not just the material being taught but also in their students. They will be able to understand students' interests, joys and concerns. This is not a ubiquitous quality in teachers, and even if possessed it is difficult to display. However, proper use of this anatomy, whether at a conscious or subconscious level, will have a profound impact on students' learning and will certainly cement the student-teacher relationship into an effective learning bond. The more that this empathy can be displayed (the cardiac 'stroke volume,' so to speak) the better the relationship will be.

When using their heart, ACEs are also clearly establishing their ability to respect students' perspectives in the learning process. Medical students are adults, and adults generally prefer to play an active role in their own learning.[2] The ACE therefore makes allowances for this reality throughout the learning process, such as by asking the learners what they *themselves* feel their learning needs are. Medical educators who are able to rapidly pick up on the empathic advantages of this phenomenon have, metaphorically speaking, developed a faster 'heart rate'. Teachers with superlative stroke volumes and heart rates will have the best empathic 'cardiac outputs'; it is these ACEs whom students will respect and use as role models, surely one of the highest compliments a teacher can receive.

The complete teacher is one who is accomplished. What is meant by this term, though? Is an accomplished teacher one who is extensively decorated with various degrees and multiple publications attesting to his or her experience? Although certainly important, these achievements do not do justice to the potential depth of the word 'accomplished.' Despite the anatomical fundamentals behind the talents and traits of the ACE, effective teaching remains an inherently complex process, one which titles or honours cannot sufficiently quantify. The accomplished teacher is one who understands that learning is what remains after most of the teaching is forgotten, and then still proceeds whole-heartedly with this daunting task. This is no mean feat, and sustained teaching excellence only comes at the expense of a great deal of time investment and long-term dedication. Such educators, be they highly decorated or not, understand this challenge; they are able to apply themselves to teaching in a versatile manner and will often consequently see more successful learning and enjoyment in their students.[3] Such a teacher may truly have all the components of complete teaching that works in harmony, yet would also still be thinking of ways to make them work better. This sort of thinking, this rare sort of metacognition, is the purview of the anatomically correct educator - the complete teacher.

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# 1998 OMSW at the University of Toronto

Charlene Fell, MSc. (OTO)

The Ontario Medical Students' (OMSW) Weekend is an annual conference, which brings together students from all five Ontario medical schools for career-related seminars and workshops and social events. OMSW 1998 was hosted by the University of Toronto Medical Society from January 23 to January 25, 1998. The theme of the conference was *Everything You Wanted to Know About Being a Physician...but Were Afraid to Ask*. Over 250 students, speakers, and industry representatives attended the event.

The conference opened on Saturday morning with a keynote address by Dr. Ted Boadway, Executive Director, Department of Health Policy, Ontario Medical Association. His talk, entitled *"The Future is so Bright, You'll Have to Wear Shades,"* addressed issues that students will eventually face with the current and continuing health reform in Ontario and the rest of Canada.

Following Dr. Boadway's opening address, students attended concurrent workshops and seminars on a variety of topics. The seminars addressed topics such as *"Combining Conventional and Naturopathic HIV/AIDS Treatment", "Primary Care Payment Systems in Ontario," "Challenges Facing New Doctors,"* and a talk by Toronto Sun Health Care Columnist Christina Blizzard. Several panel discussions allowed students to interact with physicians and residents and addressed topics such as surviving the CaRMS match, living and practising medicine in rural and underserviced areas, and gender issues. MD Management held a workshop on managing personal finances and on financially managing a medical practice. In addition to these workshops, students had an opportunity to learn surgical skills in three popular surgical skills clinics: an IV Line Clinic, a Suture Clinic, and a Knot-tying Clinic.

On Saturday afternoon there was a poster session hosted by Educating Future Physicians for Ontario (EFPO) which showcased student-initiated extra-curricular projects which addressed various health care needs of the community. Some of the projects, such as the University of Toronto's International Health Program and McMaster's Physicians for Global Peace Program, and Ottawa's Student Health Initiative focused on global issues; other projects, such as the University of Toronto's Let's Talk Sex and Let's Talk Science programs addressed the needs of local and inner-city communities. The poster session provided students from these programs an opportunity to share experiences with each other and with interested students attending the conference.

The second keynote address on Saturday was hosted by EFPO and given by Dr. Brian Hodges, Assistant Professor, Department of Psychiatry, University of Toronto. His talk, entitled *"Universities and the Underserviced North: Is It Our Problem?"* challenged students to think about whether the goals of universities should address the values and needs of society. He also challenged students to contemplate how universities, and medical schools in particular, can work towards decreasing the number of areas in Ontario which are underserviced by health care professionals.

On Sunday morning two concurrent sessions were offered. *"Surviving Politics in Medicine"* was a panel discussion with several provincial politicians, members of the OMA, and medical students who are involved in politics through the Canadian Federation of Medical Students (CFMS). MD Management also offered a second session of their popular financial planning workshop. The conference closed with a keynote address by Joshua Tepper, a third year medical student at McMaster University and President of the CFMS. Mr. Tepper gave students an overview of the CFMS, its goals and objectives, and plans for the future. He also spoke passionately about the unique stresses associated with pursuing a career in medicine. He asked the audience to observe a moment of silence in respect of those students who had committed suicide while in medical school. He also spoke about inadequate support services for medical students and the lack of knowledge among medical school faculties with respect to the needs of medical students in times of stress. Mr. Tepper will be studying this problem in the near future and ended his talk with several suggestions to improve student support services and decrease student stress.

The OMSW 1998 Organising Committee would like to thank our sponsors who so generously supported this year's conference. We would like to thank our speakers who generously donated their time to present talks, participate on discussion panels, or teach students surgical skills during the conference. We would also like to thank the University of Toronto's Faculty of Medicine and its staff for their unending support and assistance in this and all student-initiated events. We look forward to seeing everyone next year for OMSW 1999 at McMaster University in Hamilton, Ontario.

# Medical Student Research Day

Adrienne Chan, BSc. (0T0)

The 12th annual Faculty of Medicine Medical Student Research Day was held on Tuesday January 13, 1998. This event, which is meant to promote and encourage medical student interest in academic research, featured several keynote speakers as well as 76 poster presentations by students enrolled in the undergraduate medicine program and the MD/Ph.D program. The quality and variety of the research presented, which ranged from basic science investigation to the study of clinical applications in hospitals and in the community, was reflected by the seven winners chosen to be recipients of the George Brown Memorial Award. The award categories were based on the type of research carried out as well as the previous academic research experience of the presenters.

## The Winners

Catherine Mason, MSc. (year 4 MD/Ph.D), won the MD/Ph.D award. Ms. Mason was supervised by Dr. Marlene Rabinovitch, Department of Pediatrics, for: *HJV-liposome mediated gene transfer with a plasmid encoding decoy RNA containing the 3' untranslated regulatory region of fibronectin mRNA inhibits neointimal formation in the ductus arteriosus.*

Gihane Wasfy, MSc. (0T0) won the Basic Research (Graduate) award. Ms. Wasfy was supervised by Dr. Linda Penn, Department of Medical Biophysics, for: *Characterizing the molecular mechanisms of Lovastatin induced apoptosis.*

Ian Bookman, BSc. (0T0), won the Basic Research (Undergraduate) award. Mr. Bookman was supervised by Dr. Shaf Keshavjee, Department of Surgery, for: *Adenoviral-mediated Interleukin-10 gene transfection: Optimal dosing in a rat model.*

Danielle Gervais-Fagnou, MSc. (0T0), won the Clinical Research (Graduate) award. Ms. Gervais-Fagnou was supervised by Dr. Paul Goss, Department of Medicine, for: *Breast cancer in women following superdiaphragmatic irradiation for Hodgkin's disease.*

Corwyn Rowsell, BSc. (0T0), won the Clinical Research (Undergraduate) award. Mr. Rowsell was supervised by Dr. Mark Cattral, Department of Surgery, for: *The outcome of kidney transplant alone versus synchronous pancreas-kidney transplantation in Type I diabetics.*

The Health Care Research (Graduate) Award was shared by Dave Robertson, MPhil., Sofia Ahmed, Lisa Hicks and Yulin Lin (9T9) who presented a student initiated project on: *Ethical dilemmas in clerkship.*

Lisa Hicks, BSc. (9T9) was the winner of the Health Care Research (Undergraduate) Award with her presentation on: *Pregnant or parenting women with drug addictions: Factors affecting treatment maintenance.*

Catherine Mason and Gihane Wasfy, the top-rated award winners, were chosen to represent the Faculty at the 38th annual Medical Student Research Forum (USA) in Galveston, Texas. In addition, the Department of Medicine chose Danielle Gervais-Fagnou, the top-rated student supervised by one of its members, to attend the same meeting.

# A Coagulative Conundrum

prepared by
Jonathan Grynspan, BSc. (0T0)
and Paul Chong, MD

## Case Presentation

A 50 year old woman was transferred from a community hospital to The Toronto Hospital - General Division because of fever, confusion, multiple neurological deficits, and a pre-gangrenous leg.

The patient presented to a community hospital 3 months prior to the current admission complaining of diffuse soreness in both legs. She had a remote history of post-partum deep vein thrombosis (DVT) and varicose vein stripping. She had been on a vacation that involved a four hour plane ride and extensive car travel six weeks prior to the hospital visit. Ultrasound Doppler studies were negative for DVT. She was placed on non-steroidal anti-inflammatory agents (NSAIDs) and instructed to wear supportive stockings. Over the ensuing four weeks, the patient experienced transient episodes of confusion, slurring of speech, blurred vision, diplopia, and numbness of her hands and feet. She also developed intermittent low grade fever, shortness of breath, and abdominal discomfort.

Five days before admission to this hospital the patient presented to the community hospital with confusion, weakness, arthralgia, and diffuse abdominal pain. The temperature was 38°C, the pulse, respiratory rate and blood pressure were normal. On neurological exam the patient was alert and oriented to person, location and time. There was dysphasia, right homonymous hemianopia, right pronator drift and loss of fine finger movements in the right hand. Muscle power, deep tendon reflexes and sensory exam were normal. Her toes were downgoing. Examination of the head, eyes, ears, nose and throat was unremarkable and there was no nuchal rigidity. Exam of the extremities showed several splinter hemorrhages in the fingernails, petechiae in the legs and very poor perfusion to the toes. The rest of the exam was within normal limits. Laboratory tests and a lumbar puncture were performed and are documented in Tables 1, 2 and 3. A chest radiograph was considered normal. EKG and computed tomographic (CT) scan of the head were normal. The patient was seen by a neurologist. The working diagnosis was viral encephalitis. She was started on intravenous Acyclovir, Ceftiraxone and Methyl-Prednisolone and was admitted for further investigation.

Additional laboratory tests performed over the following days were as follows: ANA was weakly positive with a homogeneous staining pattern; C-reactive protein (CRP) was elevated (177 mg/L). Rheumatoid factor (RF) was negative; values for complement factors C3 and C4 as well as thyroid stimulating hormone (TSH) were all within normal limits; blood cultures were negative.

On the second hospital day a transthoracic echocardiogram with doppler revealed a grade one left ventricle, trace mitral regurgitation and no clots, valvular vegetations or other valvular abnormalities. Ultrasound of the abdomen showed multiple hypoechoic areas with coarse texture throughout the liver consistent with metastases. A nonenhanced CT scan of the head was normal. Radionucleotide (HMPO) brain scan, performed on the third hospital day demonstrated normal symmetrical perfusion bilaterally. On the fourth hospital day a CT scan of the head was repeated with and without contrast. A number of zones of decreased attenuation, posteriorly in the parietal lobes, were visualized (Figure 1). CT scans of the abdomen with and without contrast, as well as CT scans of the pelvis with contrast were performed. Innumerable small areas of decreased attenuation, with a maximum diameter of 1 cm, were seen scattered throughout both the right and left lobes of the liver (Figure 2). Relatively large, wedge shaped areas of decreased

enhancement involving both renal cortices in a somewhat spokewheel fashion were also noted (Figure 2). The gallbladder, biliary tree, pancreas, aorta as well as both adrenal glands all appeared normal. A diagnostic procedure was performed, however, the results were not available at the time.

**Table 1**
**Hematological Laboratory Values**

| Variable | Value | Range |
|---|---|---|
| Hemoglobin (gm/L) | 135 | 120-160 |
| Mean Corpuscular Volume ($\mu m^3$) | 78 | 80-97 |
| Erythrocyte sedimentation rate (mm/hr) | 7 | 0-20 |
| *White-cell count ($10^9$/L)* | *18* | *4-11* |
| *Platelet count ($10^9$/L)* | *131* | *140-450* |
| Partial-thromboplastin time (sec) | 27 | 23.5-32.5 |
| *Fibrinogen (gm/L)* | *reduced* | |
| *Fibrinogen degradation products (mg/L)* | *elevated* | |
| *Bleeding time (min)* | *>15* | *2.5-9.0* |

*values of particular interest are in italics in all tables*

**Table 2**
**Blood Chemical Values**

| Variable | Value | Range |
|---|---|---|
| Sodium (mmol/L) | 134 | 136-146 |
| Potassium (mmol/L) | 4.1 | 3.6-4.9 |
| Chloride (mmol/L) | 103 | 100-109 |
| Carbon dioxide (mmol/L) | 23 | 24-30 |
| Glucose (mmol/L) | 6.5 | 3.2-6.4 |
| Urea (mmol/L) | 5.5 | 2.7-7.5 |
| Creatinine (µmol/L) | 105 | <133 |
| *Lactate dehydrogenase (U/L)* | *1298* | *120-230* |
| *Aspartate aminotransferase (U/L)* | *200* | *<38* |
| *Alanine aminotransferase (U/L)* | *181* | *<38* |
| *Alkaline phosphatase (U/L)* | *181* | *36-92* |
| *Creatinine phosphokinase (U/L)* | *161* | *10-70* |

**Table 3**
**Lumbar Puncture Values**

| | |
|---|---|
| Red cells (/µl) | 0-2 |
| White cells (/µl) | 0-6 |
| Protein (g/L) | 0.15-0.45 |
| Glucose (mmol/L) | 2.8-4.2 |
| Gram stain | negative |
| Culture | negative |

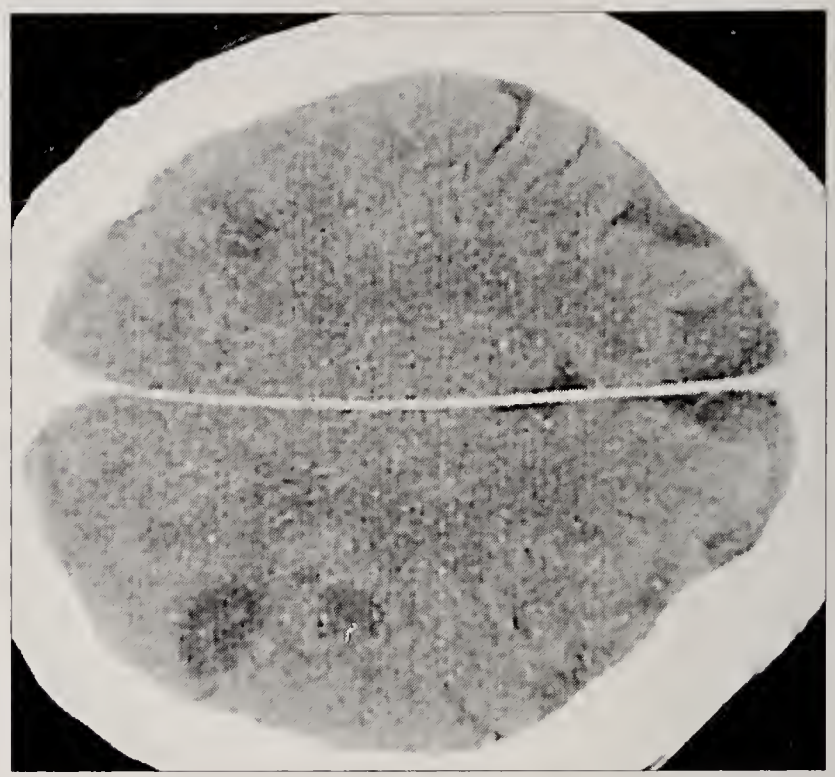

FIGURE 1. *Enhanced CT scan of the brain showing a number of zones of decreased attenuation posteriorly in the parietal lobes.*

FIGURE 2. *Enhanced CT scan of the abdomen showing small areas of decreased attenuation throughout the liver. There are also large wedge shaped areas of decreased enhancement involving the renal cortex bilaterally.*

The patient continued to deteriorate in hospital. She was transferred to The Toronto Hospital - General Division on the fifth hospital day for further investigations and management. The patient had a three month history of hypothyroidism. She was not an intravenous drug abuser and did not have recent dental work. There was no history of musculoskeletal or connective tissue disease. She was currently on L-Thyroxine, in addition to Acyclovir, Ceftriaxone, Methyl-Prednisolone and Cloxacillin which were administered in the other hospital.

The patient was agitated and confused. Temperature was 38°C, the pulse was 70, the blood pressure was 150/75, oxy-

gen saturation was 95% on room air. Examination of the head, eyes, ears, nose and throat showed no nuchal rigidity, pallor, jaundice or cyanosis. Respirations were rapid and deep, closely resembling Kussmaul breathing. A grade one systolic murmur was heard along the sternal border. On neurological examination, the patient showed no spontaneous limb movements. Muscle tone and deep tendon reflexes were normal. There were diffuse petechiae and purpura in her extremities. Her right leg was cold, mottled and showed poor capillary refill. Popliteal and dorsalis paedis pulses were absent. The rest of the examination remained unremarkable.

**Table 4**
**Hematological Laboratory Values**

| Variable | Value | Range |
|---|---|---|
| *Hemoglobin (gm/L)* | *109* | *120-160* |
| *Mean Corpuscular volume ($\mu m^3$)* | *79* | *80-97* |
| Reticulocytes ($10^9$/L) | 95 | 40-110 |
| *Haptoglobin (gm/ml)* | *.34* | *0.4-3.36* |
| *White-cell count ($10^9$/L)* | *22* | *(4-11)* |
| *Platelet count ($10^9$/L)* | *37* | *140-450* |
| INR (sec) | 1.9 | 0.88-1.1 |
| Partial-thromboplastin time (sec) | 29 | 23.5-32.5 |
| *Fibrinogen (gm/L)* | *reduced* | |
| *Fibrinogen degradation products (mg/L)* | *elevated* | |

**Table 5**
**Blood Chemical and Serological Values**

| Variable | Value | Range |
|---|---|---|
| Sodium (mmol/L) | 144 | 136-146 |
| Potassium (mmol/L) | 4.7 | 3.6-4.9 |
| Chloride (mmol/L) | 114 | 100-109 |
| *Carbon dioxide (mmol/L)* | *15* | *24-30* |
| Calcium (mmol/L) | 2.0 | 2.10-2.65 |
| Magnesium (mmol/L) | 1.1 | 0.70-1.1 |
| Total Protein (g/L) | 60 | 63-84 |
| *Albumin (g/L)* | *31* | *37-48* |
| *CRP (mg/L)* | *81* | *<8* |
| C3 (g/L) | Normal | |
| C4 (g/L) | Normal | |
| Lactate (mmol/L) | 1.9 | 0.6-1.7 |
| *Urea (mmol/L)* | *18* | *2.7-7.5* |
| *Creatinine (mol/L)* | *195* | *<133* |
| *Lactate dehydrogenase (U/L)* | *690* | *120-230* |
| Bilirubin (mol/L) | 13 | <20 |
| *Aspartate aminotransferase (U/L)* | *228* | *<38* |
| *Alanine aminotransferase (U/L)* | *147* | *<38* |
| *Alkaline phosphatase (U/L)* | *274* | *36-92* |
| Alpha fetoprotein (µg/L) | <5 | <30 |
| *Creatinine phosphokinase (U/L)* | *13460* | *10-70* |
| CK-MB (µg/L) | 280 | <5% CK |
| HBsAg | negative | |
| HBsAb | positive | |
| HCV-Ab | negative | |

Urinalysis yielded high levels of red blood cells and protein, with heme-granular casts. A peripheral blood smear demonstrated red cell fragments, spur cells, basophilic stippling and polychromasia. The results of other laboratory tests and measurements of arterial blood gasses are shown in Tables 4, 5 and 6. The A-a gradient was calculated as 44. A transesophageal echocardiogram was performed. Multiple masses suggestive of vegetations were seen attached to the posterior mitral valve leaflet.

**Table 6**
**Arterial Blood Gases**

| | Value | Range |
|---|---|---|
| pH | 7.44 | 7.35-7.45 |
| pC02 mmHg | 27 | 34-45 |
| pO2 mmHg | 71 | 80-100 |

On the second hospital day the results of the diagnostic procedure became available.

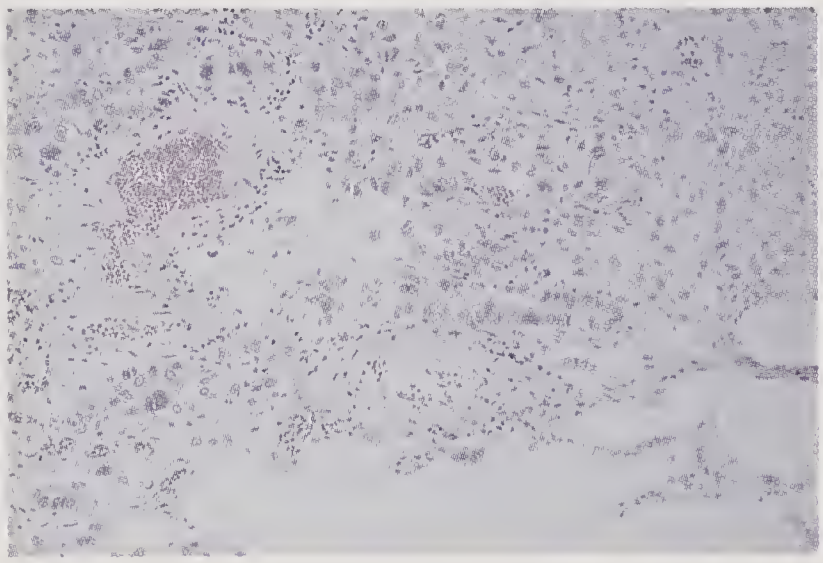

FIGURE 3. *Histological section of lung showing adenocarcinoma. The pulmonary air sacs are lined by cells with an ample faintly eosinophilic cytoplasm and basally situated nuclei.*

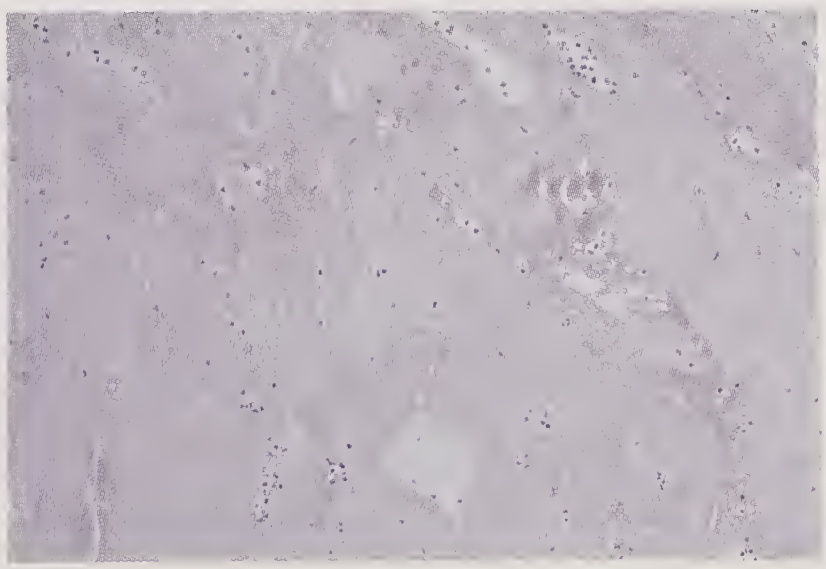

FIGURE 4. *Histological section of mitral valve showing bland fibrin thrombus with occasional neutrophils.*

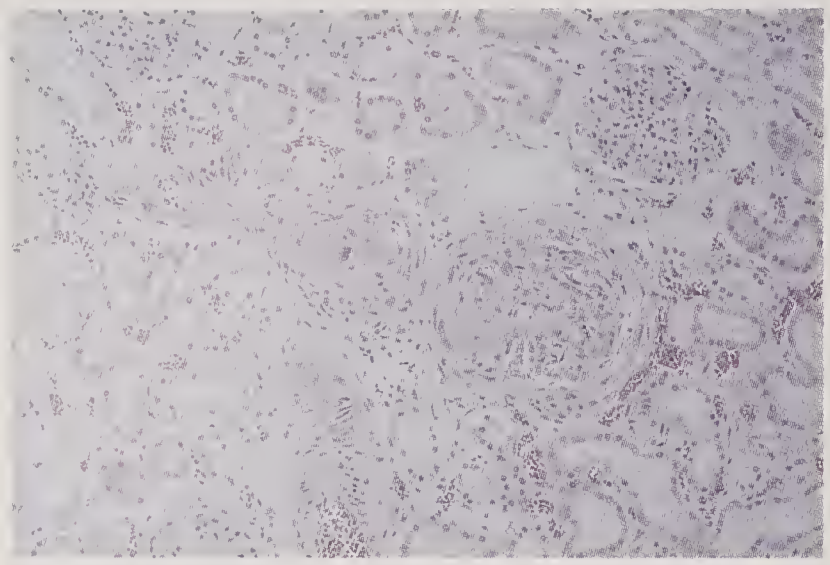

FIGURE 5. *Histological section of the kidney showing fibrin thrombi occluding small arterioles and glomerular capillaries.*

## CPC Discussion

Dr. Steven L. Shumak*: May we begin by reviewing the results of the medical imaging studies.

Dr. Scott Good: CT scans of the brain taken on the fourth day at the community hospital show several zones of ring enhanced hypodense areas in the grey white interface of the parietal areas bilaterally. These may represent multiple foci of cerebral infarction, inflammation or vasculitis. CT scans of the abdomen taken on the same day reveal numerous areas of decreased attenuation scattered throughout both lobes of the liver that are consistent with low density lesions previously detected in the liver by abdominal ultrasound. These lesions may represent extensive and diffuse hepatic metastases, diffuse inflammatory change or microabscesses. Wedge shaped areas of decreased enhancement in both renal cortices, seen on the same abdominal CT scans, are suggestive of infarction or vasculitis.

Dr. Shumak: This young and previously healthy woman presented with a brief and apparently accelerating illness characterized by symptoms and signs involving the CNS, abdomen, liver, kidneys and extremities. All of this was occurring in the setting of a rapidly developing anemia and thrombocytopenia. Are these symptoms, signs and laboratory abnormalities all manifestations of a single disease? Or, must we be forced to invoke the presence of multiple diagnoses to account for her presentation?

Occam's razor is a now famous dictum issued by one Sir William of Occam (also spelled Ockham) in the early XIVth century. Although variations on his adage exist, he is quoted as saying "plurality should not be assumed without necessity."[1] To paraphrase, "one should always seek a single unifying explanation for observed phenomena."** Occam's admonition has become a guiding principle in clinical medicine and I shall approach this case with his aphorism in mind. Indeed, I believe that all of the multiple and varied findings in the present case can be traced back to a single underlying disease entity.

Although the clinical examination is full of clues in this complex case, I would like to begin my approach by considering the nature of her hematological problem. We are told that shortly after her transfer to the Toronto Hospital - General Division an anemia developed, and that her peripheral blood smear demonstrated fragmented red cells and polychromasia. The presence of red blood cell fragments is essentially diagnostic of intravascular hemolysis due to mechanical trauma to the red cells. That intravascular hemolysis is present is also supported by the fact the patient's serum haptoglobin level is depressed (haptoglobin is used to bind and transport the free hemoglobin released by intravascular hemolysis) and that her serum LDH is elevated (LDH is released by hemolysed red cells). In uncomplicated traumatic hemolysis, one also expects to find an elevated reticulocyte count. I assume that the reason she did not have a more brisk reticulocytosis was that there was an underlying process suppressing her marrow. I will return later in my discussion to consider the nature of this underlying process. The major causes of traumatic hemolysis are listed in Table 7, and I will comment on each as it relates to the present case.

**Table 7**
**Major Causes of Traumatic Hemolysis**

- mechanical heart valves/vessel grafts
- accelerated hypertension/eclampsia
- vasculitis e.g. SLE, PAN
- thrombotic microangiopathies
- disseminated intravascular coagulation

The cause of the mechanical trauma to the red cells that occurs in the setting of a mechanical heart valve or large vessel graft is self-evident. This woman did not have a mechanical heart valve or a vessel graft. In conditions such as malignant hypertension, eclampsia and related disorders there is endothelial damage and reaction which leads to deposition of fibrin in the microvasculature. This leads to deposited traumatic hemolysis when the red cells encounter the deposited fibrin. This woman's blood pressure was not high and eclampsia is not a relevant condition.

In some forms of vasculitis, the associated vascular and perivascular inflammation lead to intraluminal fibrin deposition and compression of the lumen respectively. Both phenomena can contribute to mechanical hemolysis (Of course,

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**It has been rumoured for centuries that Sir William died of multiple causes!

there are other more common mechanisms for hemolysis occurring in the setting of vasculitis such as antibody mediated red cell destruction). Could this woman have had a vasculitis? Indeed, the multisystem nature of her illness is consistent with a vasculitic process. Nevertheless, we are told that her ESR was in the normal range, her ANA was only weakly positive, her rheumatoid factor was negative and importantly, that her serum complement levels were normal. This set of negative serological results can be considered to rule out active systemic vasculitis. Two entities remain, therefore, in our list of causes of traumatic hemolysis – thrombotic microangiopathies and disseminated intravascular coagulation (DIC). I shall consider each in turn.

Thrombotic microangiopathy is a term referring to several conditions all characterized by inappropriate and accelerated platelet activation as well as fibrin deposition in the microvasculature.[2] Consequently, platelets are consumed and thrombocytopenia develops, and hemolysis occurs as a result of mechanical damage to the red cells as they encounter the intraluminal fibrin deposits. The two prototypes of thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Since the latter disease is, by definition, associated with acute renal failure, and since this woman was not in acute renal failure, I shall not consider HUS further. Moreover, there is a growing consensus that TTP, which I will discuss, and HUS, are different manifestations of a single underlying pathologic process.[2,3]

TTP is an uncommon disease of uncertain etiology most frequently affecting young to middle aged women. The pathogenic hallmark of TTP is widespread microvascular thrombosis with pathological examination showing arteriolar filling by conglomerates of fibrin and platelets. As explained earlier, this type of process will lead to traumatic hemolysis and platelet consumption. The widespread microvascular thromboses in TTP account for its clinical findings. Certain tissue beds such as in the brain and kidney seem to be particularly susceptible to thrombosis. The diagnosis of TTP is made clinically on the basis of its classic pentad: fragmentation hemolysis as evidenced by the peripheral blood film, thrombocytopenia, fluctuating neurologic signs, renal dysfunction and fever. Arthralgias and abdominal pain are also common manifestations of the disorder. All of these features were present, to some degree, in the case under discussion. In fact, the transient neurologic symptoms experienced by this patient - confusion, aphasia, hemianopia, and hemiparesis are typical for TTP. It is therefore impossible to rule out TTP as a contributing cause to this woman's presentation. However, it is distinctly uncommon for TTP to be associated with the type of coagulation abnormalities that were also present in this case. Hence, rather than infer that this woman has a rare manifestation of a rare disease (coagulation abnormalities in TTP), I would prefer to conclude that TTP alone cannot account for her entire clinical picture. I will use Occam's razor then, to slice TTP off the list of diagnostic candidates.

Before considering any other diagnostic possibilities, I will summarize the coagulation abnormalities present in this case. By the time of her transfer, this woman had an elevated INR, a reduced level of fibrinogen and elevation in her fibrin(ogen) degradation products (FDP). Her PTT remained in the normal range. As mentioned earlier, she had thrombocytopenia.

FDP are produced when plasmin acts on fibrinogen or fibrin to dissolve clots. Recognizing that clot lysis and clot formation are tightly linked, one sees that plasmin activation actually mirrors clot formation. Hence, FDP will be present in any setting where clots are/have been formed. Accordingly, the presence of high levels of FDP can be viewed as a surrogate marker for high rates of clot formation. The elevated FDP in the case under discussion, therefore, allows us to conclude that she had increased rates of clot formation. Yet, we are told that her INR was elevated and fibrinogen low. How does one reconcile elevated rates of clot formation with decreased levels of an essential clotting factor and an elevated INR? The patient must be clotting to such a degree that she is consuming clotting factors at a rate that exceeds their production. A similar mechanism can explain her thrombocytopenia. She has, therefore, a consumptive coagulopathy, the prototype of which, disseminated intravascular coagulation (DIC), also happens to be the remaining entry on our list of causes of traumatic hemolysis.

DIC refers to a spectrum of states characterized by uncontrolled or unregulated intravascular coagulation where the usual balance between procoagulant, anticoagulant and fibrinolytic processes is lost.[4] With coagulation proceeding unchecked, coagulation factors (fibrinogen) are consumed. In addition, thrombin that is generated by the DIC activates the fibrinolytic pathways. Together, these may result in an associated tendency for hemorrhage. Thus, the term DIC is somewhat of a misnomer. There is, simultaneously, a tendency for *both* disseminated coagulation and hemorrhage. DIC exists in two forms — an acute, fulminant type and a chronic, compensated, low grade form. The hemorrhagic tendency is negligible in chronic DIC, but prominent in the acute fulminant form of DIC. A partial list of causes of DIC is given in Table 8.

**Table 8**
**Some Major Causes of DIC**

- metastatic cancer, leukemia
- septicemia, viremia
- amniotic fluid embolism
- transfusion reactions
- burns, massive tissue damage
- vasculitis, hemangiomata

Common to all the causes of DIC listed in Table 8 is the intravascular presence of substance(s), which activate thrombin directly or indirectly. Depending on the specific cause of DIC, there may have been direct introduction into the circulation of procoagulant material (e.g. amniotic fluid embolism, certain leukemias, adenocarcinomas) or endothelial injury with consequent tissue factor release (e.g. burns or massive tissue damage, vasculitis).

What is the cause of this woman's DIC? Review of the case

record reveals that septicemia is unlikely given the negative blood cultures. Amniotic fluid embolism and other obstetrical causes of DIC are not considerations here. She did not receive a transfusion and had not suffered from burns or massive tissue damage. We reasoned earlier that vasculitis has been essentially ruled out. Quickly we are left to consider the possibility of malignancy associated DIC. Is there evidence in the case presentation to support a diagnosis of malignancy? Clearly the answer is yes. Both the abdominal ultrasound and CT examination were highly suggestive, if not diagnostic, of diffuse metastatic disease affecting the liver.

Which cancers are associated with DIC, and which could be the culprit in this case? DIC occurs in almost all patients with acute promyelocytic leukemia. In this case, however, the findings on the peripheral blood film give no hint of that disorder. Many solid tumours, especially adenocarcinomas, are associated with DIC. Perhaps the most commonly associated is prostatic carcinoma, a disease that cannot be present in our patient. Other carcinomas associated with DIC include those of lung, pancreas, stomach, colon, breast and ovary. There is no specific symptomatology described or risk factors mentioned in the case record to point specifically to any of these entities. Likewise, the physical exam as presented provides no clues to indicate a primary site of carcinoma. A chest radiograph was normal and the abdominal CT exam did not reveal an obvious primary carcinoma either. Her age and sex do raise the possibility of either breast or ovarian carcinoma.

To this point then, we have reasoned that the patient was experiencing traumatic hemolysis secondary to DIC. In turn, the DIC was most likely secondary to the presence of an underlying adenocarcinoma. Are there features of the case that are still not explained? If so, must we invoke another diagnostic hypothesis and run the risk of nicking ourselves on Occam's razor? Or, might there still be a single unifying explanation?

I am struck by the absence of bleeding manifestations in this case. If this woman is suffering from DIC *per se,* the DIC must surely be very severe in order to cause the extreme clinical manifestations she was experiencing. However, severe DIC should also be associated with major bleeding diatheses which is not the case here. In fact, the relative absence of bleeding complications in this woman, despite the presence of DIC, suggests that her DIC is more likely to be of the compensated, low-grade type.[4] This is consistent with the fact that chronic DIC is the type of DIC more likely to accompany a solid tumour[5] – the postulated cause of the DIC in this patient. Therefore, although the DIC that is present in this woman may explain the appearance of the peripheral blood film and the abnormal coagulation values it seems inadequate to account for the severity of the clinical manifestations. In particular, chronic DIC seems an implausible explanation for the pregangrenous state of her leg, the renal cortical infarctions detected by the abdominal CT scan and the areas of cerebral infarction seen on the CT of the brain. The question arises – in a woman with carcinoma and associated low-grade DIC, what could account for such diffuse and substantial tissue infarction?

Endocarditis was clearly on the minds of the attending physicians in this case. A transthoracic echocardiogram was performed, and when it was negative, they went on to obtain the much more sensitive transesophageal echocardiogram. That test demonstrated multiple masses on her posterior mitral valve leaflet. Although there are other very rare causes of valvular masses, it is reasonable to assume they represented vegetations and that this woman had endocarditis. The presence of endocarditis clearly can explain the multiple infarctions detected by the various imaging studies noted above. In particular, the vegetations found in any type of endocarditis may dislodge and cause embolization with consequent infarction at the destination site of the embolus. Which type of endocarditis is present in this case?

Endocarditis may be due to infection of the valvular endocardium or be secondary to a non-infectious process. By far the most common cause of infective endocarditis is that due to bacterial infection, most often by Streptococcal or Staphylococcal species. The fact that a set of blood cultures was negative in this case does not rule out the diagnosis of infective endocarditis.[6] Even in Streptococcal endocarditis, a single set of cultures is positive in only about 95% of cases. If antibiotics have been given in the week prior to the blood culture determination, as occurred in this case, the sensitivity drops dramatically. Furthermore, some cases of infective endocarditis are due to organisms that are difficult or impossible to culture — so called 'culture negative endocarditis.' This occurs in as many as 5% of cases of infectious endocarditis.[6] Given this information, and acknowledging that the clinical picture in this case contained many features consistent with infective endocarditis and/or its complications (fever, valve vegetations, organ infarction, splinter hemorrhages, hematuria), the diagnosis of infective endocarditis cannot be excluded. Moreover, since antibiotic therapy is relatively benign and since untreated infective endocarditis is always fatal, one cannot challenge the attending physicians for initiating empiric antibiotic therapy as they did. Notwithstanding these points, I do not think she had infective endocarditis. Turning to Occam's razor once more, I am reluctant to invoke the presence of another distinct disease entity in this unfortunate woman. If not infective endocarditis then, could she have non-infective endocarditis? If so, can it be related to her underlying malignancy?

There are two major types of non-infectious endocarditis. One, so-called Libman-Sacks endocarditis, occurs in association with systemic lupus and/or the antiphospholipid syndrome.[7] For reasons discussed earlier, I do not believe that this woman is suffering from SLE. Could she have the primary antiphospholipid syndrome? This syndrome is characterized by the presence of so-called antiphospholipid antibodies that are associated clinically with recurrent venous and arterial thromboses as well as with thrombocytopenia.[8,9] Fetal loss is common in women with the disorder and results from placental insufficiency due to thromboses of placental vessels. The mechanism(s) by which the antiphospholipid antibodies promote thrombus formation is still incompletely understood. It is of some clinical importance to note that, paradoxically, some individuals with the syndrome actually have a prolonged PTT (the "lupus anticoagulant"). This

must not be misinterpreted to indicate that a state of anticoagulation is present. Rather, the prolonged PTT is an *in vitro* artifact that occurs because certain of the antiphospholipid antibodies in the serum of these patients bind to the phospholipid used in the PTT assay.

Certainly, this patient's multiple thromboembolic manifestations are consistent with the presence of the antiphospholipid antibody syndrome. In particular, thromboembolism involving the CNS and extremities is common in the syndrome. Moreover, if there were an associated Libman-Sacks endocarditis, with its attendant valvular vegetations, there would be yet another reason to account for the thromboemboli. However, we are not told if this woman had had fetal loss, a key marker for the syndrome, nor indeed if she even had the culprit antibodies. We do know that her PTT was not prolonged, although PTT prolongation is of low sensitivity for the antiphospholipid syndrome. Most importantly, I believe it would be unusual to see such a fulminant clinical presentation of the antiphospholipid antibody syndrome, especially in the absence of any previous unexplained thromboembolic manifestations in fifty years of apparently healthy life. Finally, the antiphospholipid syndrome would, by itself, not account for the traumatic hemolysis. Hence, although invoking the diagnosis of the primary antiphospholipid antibody syndrome might account for her non-infectious endocarditis, and possibly for the thromboembolic manifestations, it would not explain her DIC and traumatic hemolysis. Asserting the presence of the antiphospholipid antibody syndrome, therefore, would mean that, in addition to the carcinoma that does account for her DIC, I would now also be assuming the presence of yet another rare disease - primary antiphospholipid antibody syndrome. Sir William would be outraged.

I believe this woman does have, however, the other major type of non-infectious endocarditis. This type is known variously as 'non-bacterial thrombotic endocarditis' (NBTE), 'terminal endocarditis' or 'marantic endocarditis' and refers to the deposition of fibrin and platelets on the cardiac valves, where by definition, the deposits are sterile. Typically, there is both an underlying chronic DIC and an associated malignancy, just as in the present case.[10-12] The most common associated malignancy is adenocarcinoma, most often of the lung. Very rarely, NBTE develops in patients without cancer with case reports documenting its occurrence in AIDS, sepsis, burns and several other miscellaneous conditions.[10,12]

The prevalence of NBTE in patients with cancer may be greater than is generally appreciated. One study used echocardiography to demonstrate cardiac valvular vegetations in 19% of non-selected ambulatory cancer patients.[12] Autopsy-determined prevalence rates are lower, less than 9%.[10,11] This disparity may be explained by the friable nature of the vegetations of NBTE and their tendency for antemortem embolization. Systemic emboli are reported to occur in over 40% of patients with cancer-associated NBTE. There seems to be a particularly high incidence of emboli to the CNS[10,11] although essentially any organ or tissue may be affected. Treatment of NBTE is difficult although heparin may be of some benefit to prevent recurrent symptomatic thromboembolism.[10,11,13] Unfortunately, the alternative term for NBTE, 'terminal endocarditis,' conveys succinctly the prognosis of the entity. I would expect that she did poorly and imagine that we will be presented with autopsy findings in addition to those of the "diagnostic procedure." Regarding that test, I imagine that a liver biopsy was performed and confirmed the diagnosis of carcinoma.

No review of thromboembolic disease occurring in the presence of cancer would be complete without at least a passing reference to "Trousseau's syndrome." Trousseau himself described migratory thrombophlebitis occurring in the presence of gastric carcinoma. Thereafter, the syndrome bearing his name was used to denote the recurrent, multiple thromboses, both superficial and deep, that may presage the development of an occult malignancy. More recently, the use of the term has broadened to encompass essentially any clinical manifestation of the hypercoagulable state associated with overt or occult malignancy, including NBTE.[13,14] This change in definition would seem to imply that Trousseau's syndrome is nearly ubiquitous in metastatic cancer since the great majority of patients with advanced cancer have at least laboratory evidence to indicate the existence of an associated hypercoagulable state.[5,15] The mechanisms underlying the association of cancer with hypercoagulability are complex and multifactorial. The topic has been the subject of several contemporary reviews and the interested reader should consult them.[15,16]

In summary, I believe that this woman's traumatic hemolysis, thrombocytopenia, and diffuse tissue infarcts/ischemia can be explained by the presence of DIC and NBTE. Both of these processes can, in turn, be explained by the presence of an underlying malignancy. Statistical reasoning suggests that the malignancy will be an adenocarcinoma, most likely from lung. Occam would be reassured.

**Dr. Detsky:** I took care of this patient during her course in The Toronto Hospital - General Division and can supply the remainder of the history. The patient was evaluated by Vascular Surgery who performed an emergency right above knee amputation. Post-operatively the patient was transferred to the ICU where she continued to do very poorly. A decision was made to discontinue therapy. The patient expired shortly after extubation in the presence of her family. She was 50.

## Dr. Shumak's Diagnosis

1. Non-bacterial thrombotic endocarditis, with systemic embolization and infarction
2. Chronic disseminated intravascular coagulation
3. Widespread adenocarcinoma

**Editor:** How did the presence of diffuse hypoechoic liver nodules influence your clinical reasoning in this case?

**Dr. Shumak:** In this case, the presence of multiple hypoechoic liver nodules, when combined with the associated clinical findings, is essentially diagnostic of metastatic disease affecting the liver. Still, things other than neoplasia can account for multiple hypoechoic liver nodules. Multiple abscesses and hemiangiomata could give such a picture although neither could explain all the other features of this case. It may be worth pointing out, as well, that although infarction in many organs may lead to various "defects" or "nodules" on imaging studies, this is not the case for the liver. The liver has a dual blood supply which tends to protect against infarction due to arterial embolism such as might occur in endocarditis for example. If it does occur, hepatic infarction tends to be diffuse, involving vast watershed areas. The resulting pattern seen on imaging studies is not one of nodular disease. Hence, although this woman's renal, CNS and extremity lesions are probably manifestations of infarction, I do not think that her hepatic nodules can be attributed to such a mechanism.

**Jordan Weinstein:** Dr. Shumak, you were reluctant to consider infectious endocarditis (IE) further in this patient since you would have to invoke an additional, distinct disease process. However, is it possible that IE is part of a unifying diagnosis? *S. bovis* endocarditis has a strong association with GI carcinoma. In patients with *S. bovis* endocarditis a GI work-up is warranted to uncover a possible occult malignancy. But what of the converse approach? This woman has CT and ultrasonographic evidence of diffuse hepatic metastases and subsequently develops a picture consistent with subacute endocarditis. Could *S. bovis* be the culprit?

**Dr. Shumak:** Your question is inspired. I agree with all your points. *S. bovis* endocarditis is strongly associated with colonic carcinoma. Together, GI malignancy and *S. bovis* endocarditis could unify most of the features of this case. As mentioned in the discussion, a diagnosis *S. bovis* or other cause of infective endocarditis is not ruled out by the negative blood cultures.

## Pathological Discussion

**Dr. Ross G. Cameron:** The diagnostic procedure was a biopsy of the liver performed under CT guidance. Culture of the specimen was negative. Histological examination of the specimen showed effacement of normal hepatic architecture by a proliferation of large malignant epithelial cells forming small nests and infiltrating cords. Individual tumour cells displayed large pleomorphic vesicular nuclei, with prominent nucleoli. Special stains for neutral mucins were positive. Immunoperoxidase staining using antibodies directed against S100 protein, HMB 45, and alpha fetoprotein were negative. The diagnosis was poorly differentiated, metastatic adenocarcinoma of unknown primary.

**Dr. Myron I. Cybulsky:** The patient died three days after the results of the liver biopsy were known. Autopsy revealed disseminated adenocarcinoma consistent with a lung primary. The GI tract, ovaries, breast and pancreas did not have any obvious tumour. A lesion, measuring 2.5 cm in diameter with intraepithelial spread was found in the right upper lobe of the lung. There were extensive metastases to the liver forming aggregates of up to 6.2 cm x 5.0 cm x 3.2 cm. Other areas of involvement included the cerebellum, multiple vertebrae, lymph nodes (hilar, periportal, and cervical), the thyroid and the right adrenal. An incidental finding was a spindle-cell thymoma which contained foci of adenocarcinoma.

There was extensive systemic thrombotic disease. A recent thrombus was seen involving the superior sagittal sinus and its draining veins, with early venous infarction of the centrum semiovale, bilaterally. Thrombosis of the left popliteal, right femoral, peri-uterine and pelvic vessels was observed. This resulted in a pulmonary embolism to the right lung. There was a mural thrombus overlying an infarcted area of the left ventricular apex. Vegetations were seen along the line of closure of the mitral valve. Microscopic examination revealed that these vegetations were composed of thrombus with no inflammatory reaction. The underlying valve showed no evidence of destruction.

Necrosis and hemorrhage of the right insular cortex was consistent with embolic infarct. Multifocal myocardial infarctions of various ages were found associated with emboli in the coronary arterioles. The apex and anterior papillary muscle were most severely affected with infarcts approximately one week old. Moderate atherosclerosis of the LAD was considered an unlikely cause of the myocardial infarcts. There were multiple splenic and renal infarcts with arterial emboli seen in the proximity. Examination of the left leg following amputation disclosed emboli in multiple vessels associated with areas of muscle necrosis. Numerous venous thrombi of variable age were also noted. Death was attributed to multi-organ infarction secondary to adenocarcinoma.

Three pathological processes occurred in this patient; adenocarcinoma, thrombosis and systemic embolization. Metastases of a lung primary involved multiple organs including the liver, brain, vertebrae and adrenals. The disseminated carcinoma caused a hypercoagulable state predisposing the patient to thrombosis. Venous thrombosis of the superior saggital sinus resulted in ischemia and infarction of the central nervous system (CNS). Thrombotic obstruction of veins draining the left leg lead to local edema and pain. Venous thrombi also embolized to the lung producing pleural based infarction. Mural thrombosis was observed in the left ventricular apex precipitated by endothelial damage secondary to myocardial infarction. Thrombus deposition also occurred on the mitral valve. Multiple emboli with adjacent areas of infarction were seen throughout the arterial vasculature but most predominantly in the heart, brain, spleen, kidney and left leg. They most likely arose from the mitral valve vegetations or the left ventricular mural thrombus. Thrombosis is very common in cancer patients. Usually

it presents as deep venous thrombosis following chemotherapy or surgery and responds well to standard antithrombotic therapy.[14] In the mid-1880s, Armand Trousseau described a more aggressive but fortunately less common thrombotic diathesis occasionally recognized as the presenting feature of patients with occult malignancy.[10] These patients experience spontaneous recurrent or migratory venous thrombosis, arterial emboli due to non bacterial thrombotic endocarditis, or both. In such cases, the primary tumour is often difficult to establish although disseminated carcinoma is evident at autopsy. Patients with Trousseau's syndrome do not respond to warfarin and must receive heparin therapy for the rest of their lives. Potential mechanisms for the hypercoagulable state induced by tumors include the production of procoagulant material such as mucin or tissue factor and endothelial damage.

Non bacterial thrombotic endocarditis (NBTE) is most commonly found in malignancies, especially adenocarcinomas. It has also been associated with disseminated intravascular coagulation as well as a variety of other disease states.[14] Vegetations are most prevalent on the mitral valve followed by the aortic valves.[5] There is a very high (42%) incidence of visceral emboli[5] due to the superficial nature of the verrucae as well as the lack of cellular reaction and organization. Cerebral emboli are most common, typically manifesting as large or medium sized infarctions of the middle cerebral artery area.[17] Emboli to the coronary, renal or mesenteric circulation also occur frequently.

## Anatomical Diagnosis

1. Non bacterial thrombotic endocarditis of the mitral valve with systemic embolization and infarction
2. Pulmonary adenocarcinoma with extensive metastases
3. Systemic thrombotic disease


## Acknowledgements

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# Nephrology Rounds

Kelly Grant, BSc. (0T0) and Ali Islam, BSc. (9T9)

A 60 year old man was recently diagnosed with hypertension by his family doctor, having a blood pressure of 190/110 mmHg. The patient has a 75 pack year history of smoking. He was placed on hydrochlorothiazide (diuretic) and vasotec (ACE inhibitor) to normalize his blood pressure. One week after being on the medication, the patient presented to the Emergency Room feeling weak and dizzy. At this time, the patient's serum creatinine levels had doubled from a baseline level of 76 µmol/L before treatment to 169 µmol/L presently; this change indicated that he was in acute renal failure. He was taken off the medication and stabilized.

When evaluated several weeks later, the patient's blood pressure in the supine position was 185/110 mmHg. Fundoscopy revealed the following:

FIGURE 1. Image of fundus. *This figure shows signs of Grade III retinopathy. Note the flame hemorrhage, silver wiring exudate, vessel tortuocity and macular stain.*

A faint bruit could be heard over the left renal artery and the right femoral artery. No other relevant findings were found from the physical examination.

**Given this clinical history, what might be the primary cause of this patient's hypertension?**

**What tests would you order to investigate this hypothesis?**

**What procedure would you perform if your diagnosis was correct?**

Given the history of this patient, there is a strong suspicion that renal artery stenosis is the cause of hypertension. There are several clues that suggest this diagnosis:[1]

1. The patient has severe hypertension that has developed after the age of 50 years.
2. A renal bruit is audible on the left side.
3. Acute renal failure (ARF) developed after treatment with an ACE inhibitor.
4. Hypertensive retinopathy was identified.

It is estimated that the prevalence of renovascular disease is responsible for 5% of all hypertension.[2] Diagnosing renovascular hypertension is important, since it is the commonest form of curable hypertension.[3] Renal artery stenosis is most commonly caused by atherosclerosis, which usually affects men older than 55, and fibromuscular dysplasia, which usually affects women between 35 and 50 years.

The pathophysiology of renovascular hypertension can be explained by the compensatory mechanisms of an underperfused kidney.[4] The stenosed renal artery leads to a hypoperfused kidney; the kidney responds as if there was a reduction in effective circulating volume, and has several mechanisms to try to increase blood volume. These compensatory mechanisms rely on the activation of the renin-angiotensin system. The subsequent rise in angiotensin and aldosterone contribute to the development and maintenance of hypertension through fluid retention and vasoconstriction.

Patients with renal artery stenosis-induced hypertension often present in ARF 1 to 14 days after the start of antihypertensive therapy, particularly with ACE inhibitors.[5] The renal failure may be associated with hypoperfusion of the kidneys due to a major decrease in systemic blood pressure. However, even without a major reduction in systemic blood pressure, ACE inhibitors alter intrarenal hemodynamics which may result in ARF.[6] Even with low renal artery perfusion in the stenosed artery, glomerular filtration rate is preserved by the maintenance of high glomerular capillary pressures caused by angiotensin mediated constriction of the efferent arteriole. With an ACE inhibitor, the reduction in angiotensin leads to a decrease in efferent arteriolar constriction. As a result, there is a decrease in glomerular capillary filtration pressure leading to a decrease in glomerular filtration.

It is important to note that patients with bilateral renal artery stenosis or patients with only one functioning kidney and uni-

lateral renal artery stenosis are most vulnerable to ARF when put on an ACE inhibitor. One normal kidney can usually compensate for the other hypoperfused kidney. Since this patient has two kidneys, his episode of ARF suggests bilateral renal artery stenosis.

The Keith-Wegener grading system is used to describe hypertensive retinopathy. The following criteria are used to grade retinopathy:

Grade I: Arteriolar narrowing.
Grade II: A-V nicking, copper wiring, cotton wool spots, and hard exudates.
Grade III: Flame hemorrhages, retinal edema, and macular star.
Grade IV: Papilledema.

Grade III or IV retinopathy is often found in patients with renal artery stenosis. Figure 1 shows signs of Grade III retinopathy including flame hemorrhages, silver wiring, exudates, vessel tortuosity, and a macular star.

The definitive diagnosis of renal artery stenosis can only be made by angiography. However, before selecting patients for angiography, there are several non-invasive tests that can be done to identify high risk patients.[7] One such investigative tool is a renal scintigraph. This test produces a 2-dimensional image of the distribution of radioactivity in the kidneys after the internal administration of a radiopharmaceutical imaging agent. Figure 2 is a renal scintigraph of this patient.

FIGURE 2. Posterior renal scintigraphy scan.

This diagnostic test revealed that blood flow to the right kidney was 86% of normal, and blood flow to the left kidney was 14% of normal. These numbers suggest that the right kidney is more perfused than the left kidney, but the renal scintigraph does not provide information on the actual amount of blood flow to the kidneys.

Given the strong suspicion of renal artery stenosis, a renal arteriogram was performed on the patient. Figure 3 shows the results of this procedure. The arrows indicate where the stenosed regions are located. Although the left renal artery is more severely affected, it is clear that the right artery is also stenosed. The patient was therefore diagnosed with bilateral renal atherosclerosis.

The most effective treatment for this type of hypertension is percutaneous transluminal renal angioplasty, with transluminal

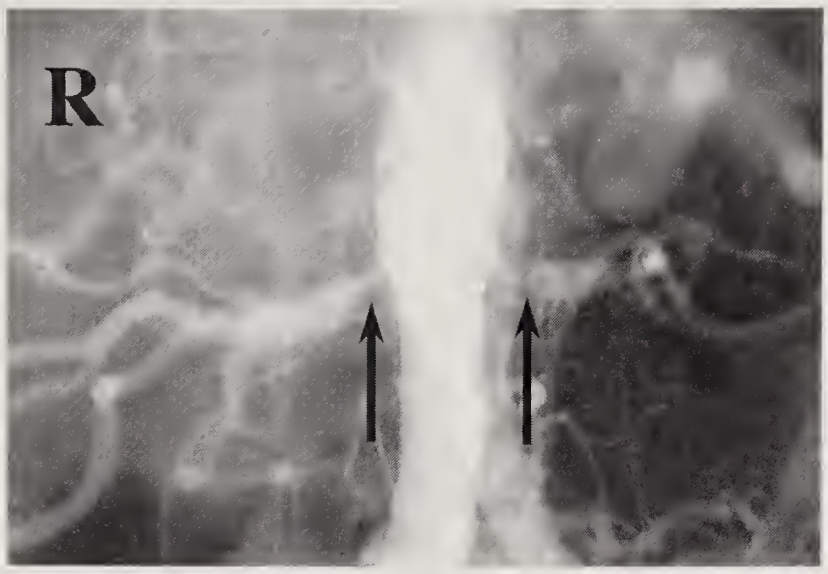


FIGURE 3. Renal arteriogram. *Arrows indicate regions of arterial stenosis.*

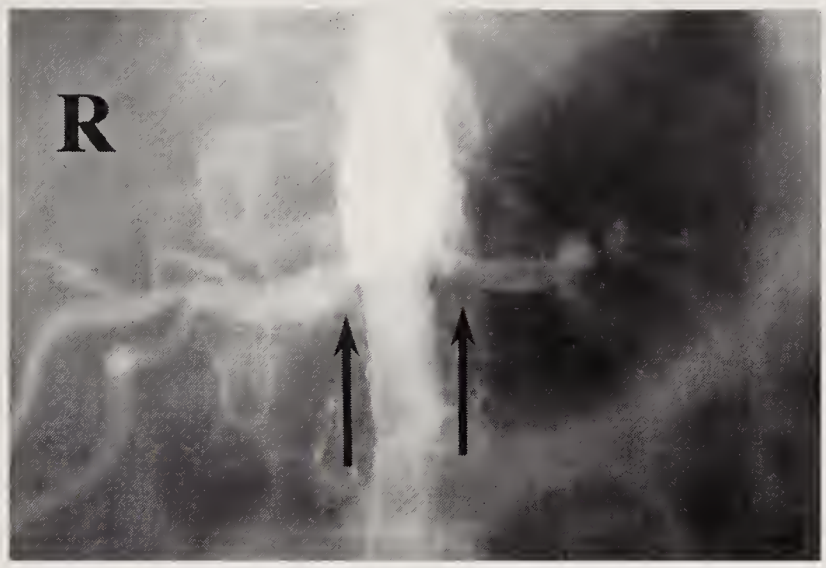


FIGURE 4. Renal arteriogram after bilateral angioplasty. *Compare with Figure 3.*

dilatations in both the left and right renal arteries. After this procedure was completed, a second arteriogram was performed, as shown in Figure 4. The success of this treatment can be seen by the marked improvement in the perfusion of both the left and right kidneys. Shortly after the angioplasty, the patient's resting supine blood pressure fell to 120/70 mmHg. This procedure had a remarkable impact on the patient. Prior to the procedure, he required three antihypertensive agents and had only modest blood pressure control; following angioplasty, he required only one antihypertensive drug. His blood pressure and renal function have remained normal and stable for six years.

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# You Can Only Find What You're Looking For

Jonathan P. Gladstone, BSc. (OTO) and
Richard M. Gladstone,* BSc. (Med), MD, FRCP(C)

**Presenter:** A 72 year old man presented to the Emergency Department at 12:30 am with a three week history of headache, worsening in the preceding 48 hours.

**Dr. Gladstone:** Sounds interesting. Headache is a common complaint, and while most headaches are benign, headaches at times can be the presenting (or only) symptom of serious and life-threatening illness. This patient's older age, and presentation to the Emergency Department at a late hour makes me suspicious already that we may be dealing with a serious problem.

**P:** Before we proceed with the case, can you provide a framework for approaching patients complaining of headache?

**Dr. G:** It takes an organized approach to differentiate amongst the many causes of headache. One useful framework is to divide headache into three broad categories. One category includes the benign primary headache syndromes such as migraine, tension-type headache and cluster headache. These syndromes have clearly defined diagnostic criteria. The second category comprises patients whose headaches are serious and secondary to underlying pathology. This group includes headaches due to infection (meningitis, encephalitis, abscess), space-occupying lesion (primary or secondary tumor), intracranial hemorrhage (subarachnoid, parenchymal, subdural), abnormalities of intracranial pressure (eg. hydrocephalus, idiopathic intracranial hypertension, or rarely intracranial hypotension), vasculitis (isolated CNS vasculitis, GCA), and other cerebrovascular conditions (ischemia, arterial dissection, venous thrombosis). The third category includes headaches that are related to referred pain from extracranial sites such as the eyes, ears, nose, sinuses, dental structures, temporomandibular joints or the cervical spine. Be mindful also of analgesic rebound and medication-induced headache as a frequent cause of chronic daily headache.

**P:** How would you begin to take a headache history from this patient?

**Dr. G:** Taking a thorough history can provide the diagnosis in most cases. The headache history requires precise details regarding the headache *onset* (gradual, abrupt, with exertion), *temporal profile* (acute, chronic, episodic, progressive, nocturnal), *location and radiation* (localized, diffuse, unilateral, alternating), *quality and severity of pain* (dull, pressure, throbbing, neuralgic), *precipitating and aggravating factors* (coughing, straining, positional changes) as well as *alleviating factors* (rest, ice, compression, massage, analgesics). It is important to inquire about associated *neurological* (focal, general) and *systemic symptoms* (fever, anorexia, weight loss, sleep disturbances), *past medical history* (infection, trauma, chronic conditions, malignancy) and medication usage.

Ask about a previous headache history (including diagnosis and prior investigations) and how the current headache is similar to or different from past headaches.

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Inquire about what treatments (mainstream and alternative) the patient has tried for the current headache. Finally, it is important to note the patient's own thoughts about the headache, what he thinks it might be, and what exactly brought him to the ER on this occasion.

P: How do you differentiate the serious and potentially life-threatening causes of headache from the more benign causes?

Dr. G: This is the most significant task of the Emergency Room clinician. The serious causes of headache are recognized by various warning signals from the history and red flags from the physical exam. Causes for concern in the history include: sudden onset headache, headache reaching maximal intensity instantly, "first or worst" headache including new or changed type of headaches, headaches that are persistent or increasing in severity, early morning onset or nocturnal headaches, headache onset with exertion, coughing, straining, or coitus, and headaches associated with nausea and vomiting, fever, infection, meningeal irritation, decreasing level of consciousness, neurological symptoms, seizures, and previous head or neck trauma. The presence of these worrisome indicators will determine the aggressiveness with which the patient will be investigated and treated.

P: The patient awoke with his headache three weeks ago and since then it has been continuous. It is always the same, localized to the right temple. It is a constant, dull pain. He has been active but lately when he tried to exert himself his headache rapidly increased in severity, then subsided with rest. It is worse when he touches his scalp or combs his hair but is relieved with an ice pack. There is no nausea or vomiting, and no visual changes or focal neurological symptoms. He had been able to carry on his usual activities until 48 hours ago when the headache began to increase in severity. He was unable to relieve the pain with Tylenol #3 from his family doctor and decided to come to the ER for pain relief and to clarify the diagnosis. In the ER, his pain was not relieved with ketorolac and oxycodone-acetaminophen.

He gave a previous history of migraine with aura, photo- and phonophobia, but he has had only one such migraine in the past twenty years. He believes that this headache is definitely different. Unlike his previous migraine, it is markedly localized and exquisitely tender to touch the painful area. Finally, the patient recalls hitting his head on a beam while working in the garage six weeks ago.

Dr. G: Headaches presenting in later life should always be taken seriously. This man has a new type of headache. It is always in the same location, not alternating sides or moving around the head, and it is continous and progressing in severity over time. These features suggest he is harbouring structural pathology until proven otherwise.

The long duration of his headache without exacerbations or remissions suggests that this is not migraine. As well, spontaneous recurrence of migraine at this age is unlikely.

One unique condition in the older patient that must be considered here is giant cell arteritis (GCA, also known as temporal arteritis or cranial arteritis). GCA is a systemic disease caused by inflammation of small and medium sized arteries that can result in persistent localized head pain and scalp tenderness. It is a medical emergency which can lead to blindness if left untreated. This diagnosis may be missed if it is not searched for specifically.

The patient also hit his head six weeks ago. Even minor head injury in an older person can produce a subdural hematoma from rupture of bridging veins into the subdural space. This patient could have a chronic subdural causing his continuous headache.

Intracranial infection can sometimes be subacute or chronic, particularly if the patient has been partially treated with antibiotics or if the infection is viral or fungal. A brain abscess takes time to develop. Often there is a primary illness elsewhere in the body (eg sinusitis, pneumonia or septicemia). This does not seem to fit the history so far.

P: What about the possibility of subarachnoid hemorrhage, arterial dissection and ischemic stroke?

Dr. G: A subarachnoid hemorrhage is an important danger to watch out for, because without prompt recognition and treatment, aneursymal rupture can be fatal. A thunderclap headache occurs with acute aneurysmal rupture and is often associated with collapse or near collapse or syncope. The headache is usually occipital-nuchal and there is meningism. Arterial occlusions and dissections can produce focal headaches of significant intensity, but the pain usually subsides after a few days. Embolic strokes are not often associated with persistent headaches and will show other physical signs on exam. I do not believe that any of these causes are likely.

Let's get back to the history. Did he have a history of ENT or sinus problems, red eyes, glaucoma or neck problems including swollen lymph nodes?

P: No.

Dr. G: Are there any systemic symptoms?

P: The patient aches all over, especially around his neck, shoulders and upper arms. He fatigues easily. He feels warm and thinks he has had a low grade fever but he did not check it with a thermometer. He has not had any recent infection, foreign travel or vaccinations.

Dr. G: Has he had any recent changes such as sleep disturbance, anorexia, weight loss, bladder or bowel disturbance, endocrine disturbance or a change of routine because of his headaches?

P: Yes, he has slept poorly and occasionally gets up at night for analgesics. His appetite has decreased and he lost five pounds in the past two weeks.

Dr. G: This sounds like polymyalgia rheumatica, a subacute condition consisting of myalgia, fatigue, anorexia and weight loss which often precedes GCA. We should ask some more questions directed at the possibility of GCA. GCA can cause ischemia in branches of the external carotid artery which can then cause pain on chewing or swallowing. These claudication symptoms are highly suggestive of GCA and very few other conditions can cause these symptoms. I would ask the patient specifically about this.

P: In response to direct questioning, the patient did reveal several interesting features. He thought he was losing hair on the ride sight of his scalp. His head hurt when he combed his hair. As well, he said his throat and tongue were sore when he talked, chewed or swallowed, so he started sucking ice cubes for comfort.

Dr. G: This increases our index of suspicion for GCA considerably. Is there anything else in his past medical history?

P: Eight years ago he had a mole removed from his back. Otherwise, he has been active and well and takes no medications.

Dr. G: Did he know the pathology of the mole?

P: Yes, it was a malignant melanoma. After excisional biopsy and axillary node dissection, he was told that he was cured.

Dr. G: We should obtain the pathology report to confirm. This could be a red herring or something important. Melanoma is known to metastasize to the brain commonly. The metastasis is usually hemorrhagic and should easily be seen on the CT scan. Although there was no nausea or vomiting (and therefore no projectile vomiting), there were some other symptoms of possible increased intracranial pressure – headache that occurs nocturnally and on awakening, as well as with straining. Obscurations of vision may occur with raised intracranial pressure. Has he had any greyouts of vision when he changes posture?

P: No.

Dr. G: What about his social and family history?

P: Both are non-contributory.

Dr. G: Let's examine the patient.

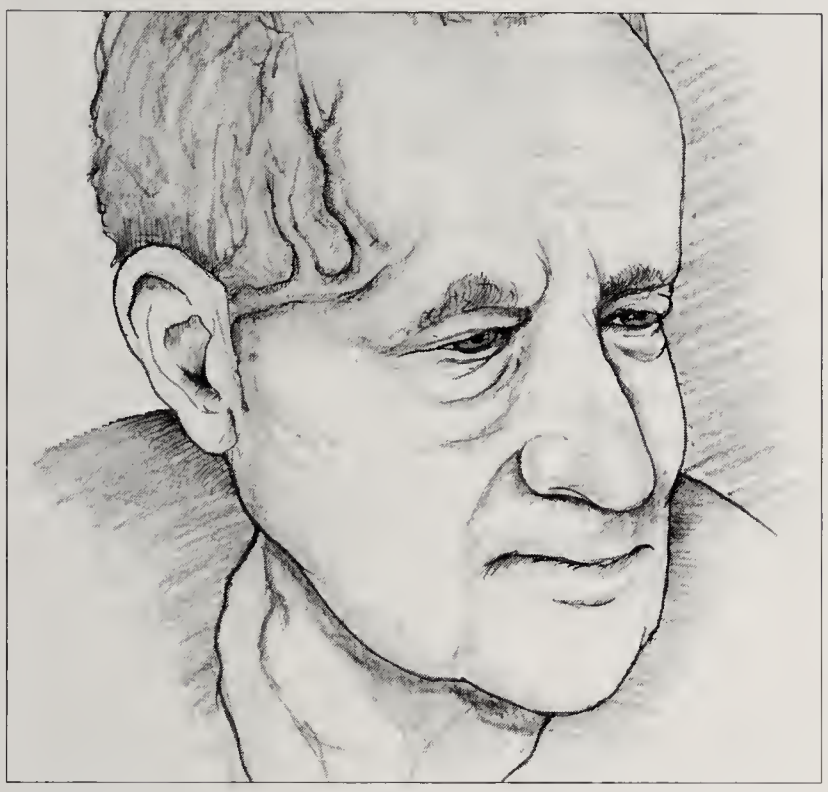
P: What do you look for when examining a patient with headache?

Dr. G: The patient's general appearance, posture, position of comfort and demeanor may be helpful but can be misleading. Migraine patients can look as ill as someone with meningitis, especially with the pallor and vomiting. The vital signs may be a clue to underlying systemic illness. Next, concentrate on the head and neck exam. I would inspect and palpate the scalp and skull for tender areas and for signs of previous trauma or surgical intervention (old scars or lacerations, and old burr holes or intracranial shunts which some patients may forget to mention). After confirming that there was no prior neck trauma, I would palpate the neck, check for neck muscle spasm, and check for signs of meningeal irritation including the Kernig and Brudzinski signs. I would transilluminate and percuss the sinuses, and check the mouth, ears, temporomandibular joints and eyes. I would auscultate over the carotid, vertebral and orbital areas for bruits (indicative of possible arterial stenosis, dissection or arterial-venous malformation). I would proceed with a relevant neurologic exam looking for abnormalities of mental status, cranial nerves, motor system, reflexes and coordination.

P: His vitals on admission were temperature 38.1° C, pulse 86 and regular, BP 140/90, respirations 12/min. He looked pale, fatigued and uncomfortable. There was no jaundice or tremulousness.

The scalp was tender over his temples and there was some hair loss over the right temple. The right temporal artery looked large and distended, yet pulsations were barely palpable (e.g. see Figure 1). The artery was firm and exquisitely tender when rolled back and forth beneath the examiner's fingers.

There were faint carotid bruits present bilaterally. Neck movements were full without crepitus or meningeal irritation, but his shoulder and neck muscles were painful on pressure. There was no cervical lymphadenopathy. Intraoral, otic and TMJ exams were normal. His eyes were not inflamed and an estimate of intraocular pressure by finger pressure on the globe over closed eyelids was normal. The remainder of the examination was normal.



Aimée Worrell

**FIGURE 1.** *A large, distended, pulseless, firm and tender temporal artery is often visible or palpable in GCA.*

**Dr. G:** The positive findings of a pulseless, distended, hard, painful temporal artery are all hallmarks of GCA. The fever is consistent with this. The tender shoulder girdle muscles suggests a preceding polymyalgia rheumatica.

What about the fundoscopic exam? It is essential in the patient complaining of headache and can be diagnostic in many instances. Specific findings to look for in any headache patient include: decreased or absent venous pulsations and papilledema as a sign of increased intracranial pressure, pre-retinal (subhyaloid) hemorrhage which can accompany subarachnoid hemorrhage, signs of hypertensive retinopathy, or features of optic nerve head ischemia.

**P:** The fundi looked normal for his age without signs of long-standing hypertension. The optic discs were normal and venous pulsations were present. Visual acuity was 20/60 in the right eye, 20/20 in the left eye. The patient does not wear glasses.

**Dr. G:** The discrepancy between his right and left eye may be a clue that he is developing ocular problems. Unless one eye is alternately uncovered and covered, patients may be unaware of any developing visual loss. The same goes for hearing too. Were any lab tests done?

**P:** The CBC, differential, electrolytes, blood sugar, urea, creatinine and calcium were all normal except for a mild normocytic anemia (hemoglobin = 106 g/L). The ESR is pending.

**Dr. G:** Normal lab values except for mild anemia are consistent with the possibility of GCA. With GCA, the ESR is usually significantly increased. It may be only slightly increased, but usually rises quickly. Occasionally the ESR can be normal. When GCA is strongly suspected, the ESR should be ordered stat. The lab may have to be contacted directly, especially if the test is ordered in off hours. What about the relevant imaging studies?

**P:** The patient's non-contrast CT scan of the head was normal. On the way back from the CT room, the patient began complaining of blurred vision in his right eye.

**Dr. G:** The normal CT makes suggests that a mass lesion, hemorrhage or subdural hematoma is very unlikely. I am concerned about his visual changes. What does he mean by blurred vision? Can you define it more specifically?

**P:** He described it as a cloud coming down over the bottom half of his right eye. When he covers the left eye, he can't see the lower half of the field of vision of his right eye. Vision in the left eye is normal.

**Dr. G:** This is called an altitudinal field defect. The causes of sudden, unilateral, altitudinal type of visual field loss include central retinal branch artery or vein occlusion, ischemic optic neuropathy, retrobulbar neuritis or, less often, retinal detachment. This would not include occipital, parietal or temporal lobe lesions which would be expected to cause contralateral field defects. Chiasmal lesions would cause bilateral field defects. Did his visual acuity change any further?

**P:** On reassessment, his visual acuity decreased to 20/80 in his right eye, down from 20/60 previously.

**Dr. G:** This is alarming. Are there any other new ocular findings?

**P:** The external and adnexal structures, lids, cornea, conjunctiva, iris and lens are clear. The anterior chamber is deep on profile. The pupillary responses are normal in the left eye, but a developing RAPD (relative afferent

pupillary defect, i.e. a Marcus Gunn pupil) in his right eye is detectable by the *swinging flashing light test.* The extraocular movements are full in all directions. The optic disc shows palid edema of the optic nerve head. The retina and macula look normal and venous pulsations are present. The arteriolar vessels appear constricted.

Dr. G: Central retinal artery occlusion and anterior ischemic optic neuropathy (AION) may not show fundoscopic changes in the first few minutes after visual loss but usually do so within hours. Retrobulbar neuritis causes pain with ocular movement, a central scotoma and loss of colour vision. Acute glaucoma would show a mid-dilated, non-reactive pupil, changes in the conjunctiva and perilimbal area, as well as increased intraocular pressure. Retinal detachment would be seen on fundoscopy. I would favour AION as the cause of the sudden visual deterioration. With AION, within a few hours there may be disc edema (early sign), peripapillary hemorrhages (middle to late sign), and cotton wool exudates (late sign) appearing. AION can be caused by embolic, occlusive or vasculitic conditions (such as GCA). Since GCA was already highly suggestive from the history and physical, the visual deterioration should be considered a medical emergency. As well, the other eye is at high risk for visual loss if left untreated. It is important to start treatment with steroids as soon as possible in this patient.

P: Why would you start steroid therapy before confirming the diagnosis with a temporal artery biopsy?

Dr. G: Vascular occlusions due to progression of an arteritis can occur suddenly and unexpectedly with the common consequence being sudden partial or complete blindness due to ophthalmic or central retinal artery occlusion. With untreated GCA, vascular occlusions can also occur elsewhere, for example coronary artery occlusion causing a myocardial infarction.

The sooner you can decrease the inflammation the better. These complications can occur even during the treatment phase if the dosage of steroids is too low or too quickly tapered. We must remember to tell the patient of the possible consequences of the untreated condition as well as the potential side-effects of steroid therapy.

P: What about the possibility of a transient ischemic attack (TIA)?

Dr. G: You're right to be concerned as well about a TIA in the distribution of the right internal carotid artery or its branches. ASA 325 mg is indicated. A chewable or regular ASA would be better than EC-ASA (enteric coated ASA) since it would have a more rapid onset of action. A carotid doppler ultrasound may be helpful here to exclude carotid thrombosis and a source for ocular emboli.

P: The patient's ESR came back elevated at 104 (normal range 0-20 mm/hr), and the patient agreed to start immediately on Prednisone. He is grateful for something to be done to stop his relentless headaches. What is the correct steroid dosage for this patient?

Dr. G: The recommended doses vary from 40-80 mg daily in divided doses. In this patient, who has unilateral visual loss, I would start with 80 mg per day orally for two weeks, followed by 60 mg for two weeks, 40 mg for two weeks, and then decrease by 5 mg every two weeks for the next month, and 2.5 mg per week thereafter, until at about 4-6 months you reach a maintenance dose of 7.5-10 mg of Prednisone per day. Some experts recommend initiating therapy with IV steroid boluses of 100-250 mg of Solumedrol q6h daily for three days when there is severe visual loss or if the other eye is also affected.

The speed of the subsequent dosage reductions reflect symptomatic and laboratory improvement, but it is best to reduce the dose slowly to avoid relapses. Steroid therapy may be required for 18-24 months and occasionally small maintenance doses are required indefinitely. The prolonged use of steroids should be associated with a strategy to minimize complications, such as prescribing vitamin D and calcium to prevent osteoporosis, and adding potassium supplements to prevent steroid myopathy from hypokalemia. Gastric mucosal cytoprotection is also useful to prevent stomach ulceration. The patient should be followed by an ophthalmologist for baseline evaluation and to detect progressive visual loss, as well as steroid-induced glaucoma and cataract.

P: What about a biopsy of the temporal artery?

Dr. G: Definitely. The biopsy should be performed over a long segment, approximately three to four or more centimetres. This would most likely involve the area of pathology (due to atheroma or inflammation). The biopsy should be generous in length to avoid a false negative result due to skip lesions. Skip lesions are areas of unaffected vessel between areas of pathology. The pathologist should sample the biopsy specimen at one millimetre intervals for maximal results.

**P:** The biopsy came back positive for GCA. Grossly, there were nodular thickenings of the vessel and microscopically there was a granulomatous inflammatory cell infiltrate in the vessel wall (with lymphocytes, plasma cells, macrophages, histiocytes, eosinophils and giant cells).

**Dr. G:** The presence of giant cells are not actually required for the diagnosis of GCA if the other typical histological features are present. These include fragmentation of the internal elastic lamina, medial necrosis, adventitial inflammation and lumenal thrombosis. These histological features can still be identified seven to ten days after steroid therapy has been started but begin to diminish thereafter.

**P:** Now that the diagnosis of GCA is definitive, could you review its salient features?

**Dr. G:** GCA is an autoimmune disorder characterized by a generalized vasculitis involving not just the temporal arteries, but also small and medium-sized arteries throughout the body. Other arteries commonly affected include branches of the ophthalmic (posterior ciliary arteries and central retinal artery), the occipital artery, and branches of the aortic arch, and even the coronary arteries. Veins are not affected.

The underlying cause is an autoimmune reaction to the intima and media of the vessels. The amount of inflammation relates to the amount of intimal elastic tissue. As intracranial vessels have only minimal elastic tissue, their involvement is rare. The inflammatory response leads to distal ischemia in the distribution of the affected vessels producing the characteristic symptoms.

The disorder is more common in females, has a mean age of onset of 71, and has an incidence of up to 6.8/100,000 in fifty-year-olds. The incidence is lower in the non-white population and higher with increasing age up to 73/100,000 in octogenarians. The condition can present abruptly or insidiously; the mean time to diagnosis is one month. GCA may be preceded by the syndrome of polymyalgia rheumatica or may also present in an occult fashion as fatigue, joint or muscle pain, claudication or with anemia or fever.

In some, there may be a genetic predisposition to developing autoimmune diseases such as GCA. Degenerating smooth muscle cells may be the inciting antigens, and immunoglobulin deposits have been found in the inflamed arterial walls; however, anti-elastin antibodies have not yet been found.

**P:** Finally, should this patient be hospitalized?

**Dr. G:** Most times hospitalization is not necessary unless there are complications. Following the biopsy and initiation of therapy, I would discharge the patient with instructions to return to my office for follow-up and weekly blood tests for the first month, and then at longer intervals thereafter. I would contact his family physician who may wish to take over his care immediately, or after I have established the proper steroid maintenance dose.

## CLINICAL PEARLS

- All persistent headaches starting anew after age 65 should be considered GCA until proven otherwise.
- Untreated, GCA can be life threatening.
- With GCA, visual loss can occur rapidly. Visual loss may occur in up to 50% of all untreated GCA patients presenting with headache.
- In patients with suspected GCA, steroid therapy should not be withheld pending temporal artery biopsy.
- A negative temporal artery biopsy does not exclude the diagnosis of GCA. Bilateral biopsy may be necessary in selected cases.
- Failure of the headache to respond dramatically to steroid therapy within several days suggests a re-evaluation of the diagnosis is necessary.

## Recommended Readings


1. Giammarco R, Edmeads J and Dodick D. (1998). *Critical decisions in headache management.* B.C. Decker Inc: Hamilton, Ontario.
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# The Middle Years

Kurt Droll, MSc. (OTO) and Ryan Foster, BSc. (OTO)

In December of 1923 the University of Toronto Medical Journal *(UTMJ)* published its first issue and began its chronicle of the ever-changing face of medicine at the University of Toronto. *From the Archives* showcases some of the most memorable and insightful research, editorials, and photographs previously published in the *UTMJ*. The highlights of the first 25 years (1923-1948) were presented in Volume 75, Number 1. In this issue we continue our retrospective look at the period we like to call, The Middle Years 1948-1972.

## The Prophet Pauling

Without a doubt the most prolific contributor to the *UTMJ* is two-time Nobel Laureate, Linus Pauling whose feature article was published in Volume 42, Number 1, November, 1964. Pauling's scientific contributions are matched by his acts of humanitarianism as evidenced by his collaborative efforts with Albert Einstein for world peace. Below are exerpts about Pauling's contributions, as well as a selection from his article which appeared in the *UTMJ*.

***Linus Pauling*** *was a member of the staff of the California Institute of Technology for more than forty years, beginning in 1922. In 1963 he joined the staff of the Center for the Study of Democratic Institutions, with an appointment that gives him freedom, as he states, to divide his efforts among the fields of principal interest to him—science, medicine, and world peace.*

*Dr. Pauling's early researches, many of which were carried out in collaboration with colleagues and students, were centered about the problem of the structure of molecules and crystals and the nature of the chemical bond. For this work he was awarded the Nobel Prize for Chemistry for the year 1954. In 1934 he and his co-workers began a series of experimental and theoretical researches in molecular biology and medicine, which in the course of time encompassed the magnetic properties of hemoglobin, the three-dimensional structure of protein molecules, the structure of antibodies and the nature of serological reactions, the discovery of the abnormal human hemoglobins that are related to certain diseases, the bearing of protein structure on the evolution of species, and the development of a molecular theory of general anesthesia.*

*Dr. Pauling's work to abolish war began in 1945, immediately after the use of atomic bombs at Hiroshima and Nagasaki, with a series of public lectures about the nature of nuclear weapons and nuclear war. It was intensified in 1946, when he became associated with Albert Einstein and seven other scientists in the Emergency Committee of Atomic Scientists. During recent years his work for world peace has for the most part been carried out in collaboration with his wife, Ava Helen Pauling. Together they have given lectures about peace in most of the states of the United States and in twenty-five other countries.*

*Hans Bethe, distinguished physicist of Cornell University and former member of the President's Science Advisory Committee, has said: "It should be realized that the limited test-ban . . . probably would not exist if it were not for the scientists . . . Pauling . . . got the Nobel Prize for his role in this—I think rightly . . . Pauling certainly had great influence on people both in this country and abroad. Without his awakening of the public conscience on this issue there would not have been any pressure on governments, and there would not have been any test-ban."*

## *The Possibilities for Further Progress in Medicine through Research* *Linus Pauling,*

One way to attack the problem of mental disease is to carry on research on the structure and function of the brain. I believe that it will be possible, perhaps within twenty years, to determine the nature of the electric oscillations in the brain that constitute consciousness and ephemeral memory, the nature of the material pattern in the brain that constitutes permanent memory, and the nature of the interactions between the electric oscillations and the material pattern. I believe that it will be possible to discover the important molecules involved in the process of thinking, to determine their structure, and in the course of time to discover what the molecular abnormalities are that lead to mental deficiency and to mental illness. Molecular biology and molecular medicine are new fields of science that can be greatly developed for the benefit of mankind.

The young man or woman who is now attending medical school and preparing to be a physician is faced with a problem that will be with him throughout his life. The nature of medical practice is going to change, more and more, during the next few decades, as the result of discoveries that are made about the human body, the vectors of disease, and the molecular basis of drug action. It will be important that the physician understands these changes that are brought about by the new discoveries. To prepare himself to follow the progress of medical research in the future, the student of medicine can do nothing better than to participate in research himself. I am accordingly pleased that I can be associated with some of the University of Toronto medical students who have been carrying on research and are publishing accounts of their work in the Research Issue of the University of Toronto Medical Journal.

## The *UTMJ* Mourns the Death of Kennedy

John Fitzgerald Kennedy was arguably the most defining political figure of the Cold War era. Few people forget where they were the moment they learned of his tragic death. The following editorial, published in Volume 41, Number 2, December, 1963, illustrates that his death had a significant impact on Canadians including medical students at the University of Toronto.

J. F. K.

The first entered posteriorly and emerged anteriorly after violating the right pleural space. He could have survived except that the second shattered the cranium and everything beneath it in the left parietal region. High integrative function was completely disrupted; life could not be sustained.

John Fitzgerald Kennedy, father, husband, millionaire, and president of the United States of America, had been slaughtered.

Each of us, no doubt, shuddered when he heard of the brutal manner in which this man had died. This death was so purposeless and violent that even the protective but sick humour of the medical student was stilled.

The executive responsibilities upon those shoulders elevated him in our eyes. The image projected grew god-like before us all. When he was sacrificed and the image shattered, we suddenly and belatedly realized our blasphemy for having diefied a mortal.

His face has now passed from magazine covers, his initials are gone from headlines, and soon his name will cease to cross the public's lips. However, men of high purpose and intelligence, public concience, and true accomplishment will long remember him. For them, he quickened aspirations into reality and began to make dreams come true.

*Wm. S.C.*

## In Search of Dr. K. Sutra

Along with the psychadelic tunes of *The Jefferson Airplane* and the disonant sounds of *Frank Zappa and the Mothers of Invention,* the 1960's brought with it sexual ideologies and practices that were hitherto unknown since the days of Caligula. This sexual revolution had both social and medical implications. During this time articles in the *UTMJ* provided commentary on this revolutionary and sometimes controversial social metamorphosis. The excerpt featured below is from an issue in January, 1969 and describes the changing view of sex in medicine.

### ***Editorial***

### *On The Sexual Revolution And Our Forthcoming Role In The Community*

Out-of-wedlock births, illegal abortions, children being raised by parents who are themselves children, or by no parents at all, broken marriages at all ages, homosexuality, venereal disease — these and other problems relating to human sexual behaviour can no longer be ignored. Whether we wish to avoid these dilemmas or not is of no consequence — we will face such issues and we will be forced to take stands.

Yet how inadequately do our medical schools prepare us as physicians to deal with the nature of human sexual behaviour. The obligation to cope constructively with these matters rests with the professionals in all fields of family service. It is not enough for us to shake our heads in moralistic judgment, and before we can properly handle our roles we must come to terms with sexuality.

Mankind, in all its history, has never been caught in the forces of such violent social change as we are today. Such movies as "The Graduate" show that it is not enough for one generation to blatantly condemn another; each one being a product of its own inconsistencies. Young people cannot rightfully be criticized for a lack of responsibility while they are being walled off in a kind of adolescent dream world where they have no chance to participate meaningfully as necessary members of a community. We can no longer propose the "double standard". It is incongruous to suggest that premarital sexual exprience for young males is necessary and inevitable and yet taking for granted that the source of such experiences will not be our own daughters or sisters. It is nonsensical to regard as non virginal the girl who for example has had a single sexual experience through rape, while praising as virginal the girl who repeatedly has every part of her body explored *PROVIDED* the male penis does not enter her vagina.

And so to be faced is the sexual revolution. From the basic need and drive that it is, just as is the desire for food or for the quenching of thirst, sex has become a tool exploited by commercial interests. Advertising orientated around sex, girlie magazines, pornographic literature and sex based movies are all on the rampage. And in so doing sex has been lost sight of as a deep form of communication in one of the greatest human relationship that we know. Understanding will come only with the recognition that sex is not something we DO but something we ARE. We have been made male and female, rather than hermaphrodites, so that we can come together in this unique fashion. Only when we realize the naturalness of this act, that it has no association with dirt, will sex fall into its proper perspective as a manifestation of the more meaningful concepts of love and above all respect.

Physicians who are on the receiving end of the troubles and burdens of human beings are going to play active roles in helping mankind to take stock of these realities. As we begin to solve the unknown realms of the physiology of pregnancy, the hormonal factors affecting reproduction and sexual drives, and the complex nature of infertility, or the as yet to be understood sequelae of contraception we will improve our medical handling of these problems. When we compound these advances with our own more mature outlooks the future role of the obstetrician and gynecologist and the physician in dealing with mankind and his necessary and inevitable social changes will indeed be a fascinating challenge. We should all be looking forward to our future roles.

H.P.D.

## Seminal Advances in Advertising

Advertisements in the *UTMJ* have been as much of a reflection of the times as the articles themselves. The volatile subject of sexual contraception did not deter the editors from 1960-1961, as they published the first advertisement promoting active contraception – the Ramses diaphragm: elegant, comfortable, and reliable.

*This advertisement appeared in Vol. 39, No. 1, Nov. 1961.*

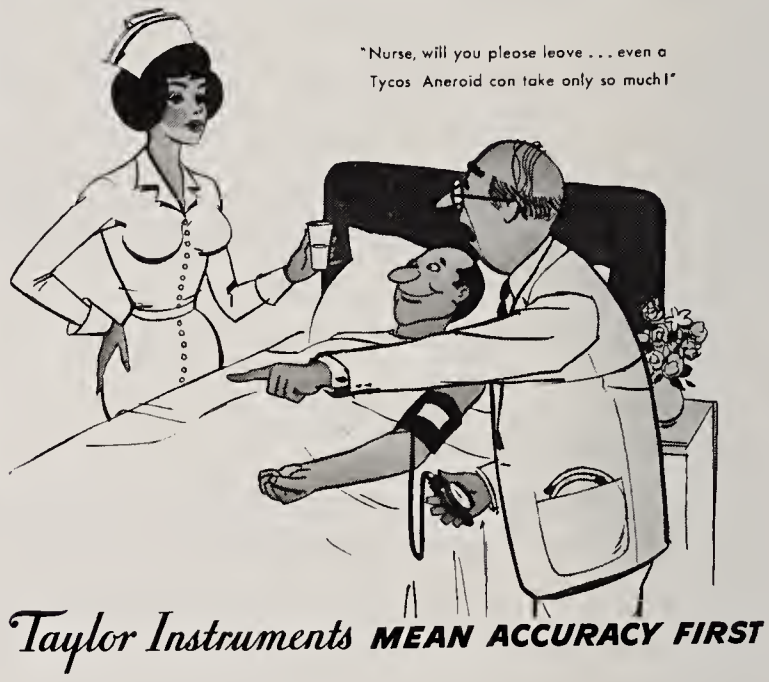
*master craftsmanship*

Master craftsmanship, traditional with RAMSES for almost a half century, stands behind the superb quality of every RAMSES Diaphragm—both the regular and the new BENDEX, an arc-ing spring diaphragm.

## Well endowed...with humour

With irony we present this advertisment from 1962. The *UTMJ* was not immune to the blatant objectification of women; however, by 1962 standards it was apparently acceptable to publish a comic of a buxom nurse whose measurments predispose patients to hypertensive crisis.

*This advertisement appeared in Vol. 39, No. 6, April 1962.*




## The Dark Ages of Enlightenment

The editorial reprinted on page 141 indicates that medicine and human sexual behaviour had reached a cross roads, and could no longer be examined separately. As a result sexual orientation was scrutinized by the medical profession. The medical authorities' perception of homosexuality was radically different than it is today; using terms like deviance, and cure, homosexuality was considered to be a treatable psychiatric disease. The following excerpt from an article entitled Homosexuality, from Volume 46, Number 1, 1968 exemplifies this view. It is hoped we have come a long way.

For decades, the prevalent social attitude toward homosexuality has been misunderstanding and contempt, reinforced by many punitive measures. Today there is an increasing interest in homosexuality evidenced by the number of papers on the subject and by public recognition of and concern for homosexuality as a social problem. The importance of the role of all physicians in understanding this problem has prompted the following consideration of its aetiology, dynamics, clinical picture, and treatment.

### DEFINITION

The term homosexual is derived from the Greek prefix homo, meaning "the same as" and not as many people suppose, from the Latin word for man. Thus, linguistically, "homosexuality" means "sex directed to the same sex." It is therefore an appropriate word to describe erotic love between two persons of the same sex, whether they be male or female. The words "lesbian" and "sapphic" are sometimes used to describe sexual relationships between women. This refers to the fact that the Greek poetess Sappho, who lived on the island of Lesbos, was herself homosexual.

### SUMMARY

In summary, homosexuality can be said to be the most common sexual deviation. Its aetiology remains unclear because of the many different phenomena grouped under the one term and the multiple factors involved in its causation.

Homosexual behaviour is prohibited in Canada by the Criminal Code but detection and presecution depend upon the circumstances, not the acts themselves.

To speak of a healthy, happy, homosexual is a euphemism. Though he or she may be creative and constructive in his work life this does not make him a healthy functioning adult. Homosexuality is engendered and persists through fear and anxiety. It is an inhibition of heterosexual expression.

The attitudes of all physicians are of primary importance in the development of a therapeutic and rational approach to this problem. Because of the opinions expressed by some physicians, a majority of homosexuals are reluctant to seek medical help; some do so with heightened anxiety.

Treatment is possible for most cases, if not in terms of cure, at least in terms of improvement of the problem situations.

## Trivial Pursuit

So often in our medical endeavors, we describe a sign, test, or procedure by its obscure eponym; and the more obscure the more impressive. Originally, eponyms served the purpose of commemorating the physicians who discovered, employed, and first taught the eponymized processes or principles. Throughout the middle years, the *UTMJ* profiled several of the more famous eponyms. We present a few choice selections in this issue as a test of our readers' knowledge of medical trivia. Go ahead, test yourself!

FREDRICH TREDELENBURG (1844-1924), also of Berlin and Leipzeig is recognized for the position used in pelvic surgery, the gluteal gait and the sign in congenital hip dislocation. His accomplishments include founding the German Surgical Society and pioneering the surgery of tracheal stricture, and gastrostomy for esophageal stricture. Trendelenburg was the first to attempt operation for pulmonary embolus (1908), a feat first successfully performed by his pupil KIRSCHNER (1924).

BARON GUILLAUME DEPUYTREN (1777 -1835), the "Brigande of the Hôtel Dieu", was born in central France. The son of a poor advocate, he was kidnapped as a boy by a rich lady from Toulouse on account of his good looks and, after reclamation, was taken to Paris and educated by a rich cavalry officer. As a medical student, however, he endured poverty, allegedly reading books by the light of oil prepared from cadavers. He became Surgeon-in-Chief at the Hôtel Dieu at the age of 36 and worked tremendously hard at teaching, operating, and seeing 10,000 private patients per year. He accumulated great wealth and was probably a most unpleasant person to meet, but his writings are delightful to read for their lucid descriptions and deductive reasoning. Like several of those mentioned here, he combined accurate clinical observation with a great interest in pathology. The best account of *Depuytren's contracture* was given by *le baron* in a lecture in 1833 and was published in the *Lancet* the following year.

JAMES PARKINSON (1755 - 1824) was principally a neurologist and described the disease which bears his name. Nonetheless, a portion of his time was devoted to psychiatry and a more extraordinary portion to revolutionary pursuits and writings; in October of 1794 he was examined before the Privy Council in connection with the "Popgun Plot" to assassinate George III. His extramedical activities also included fossil accumulation, significant papers in paleontology, and a charter membership in the Geological Society.

*Volkmann's ischaemic contracture* was named by RICHARD VON VOLKMANN (1830 - 1889), whose entire life was spent in Halle, Saxony, where his father was Professor of Anatomy and Physiology. He studied at several universities and graduated at the age of 24. Two years later he became deputy Professor of Surgery and subsequently Director. Volkmann instituted Lister's antiseptic methods at the hospital; it had previously been subject to so much infection that surgery was almost impossible. He wrote popular fairy stories and poems under the pseudonym Richard Leander, and also founded a surgical journal.

ERNEST HENRY STARLING (1866 - 1927) was hailed as one of the foremost physiologists of his era and is recognized even today as one of the greatest contributors to cardiology and haemodynamics. Born in London, he advanced quickly, entering Guy's Hospital at 16 and being elected a Fellow of the Royal Society at 33. A patron of the basic sciences, his subjects of investigation were those physiological processes which seemed capable of interpretation in terms of physics and chemistry. His laws of cardiac output marked the greatest milestone in the field since William Harvey. They did not, however, obscure his other achievements: (1) elaboration of the conditions determining vascular transudation (2) contributions to gastroenterology through his research on the neuromuscular mechanisms of intestinal movement (3) discovery of secretin (4) maintenance of a functioning mammalian kidney in vitro and subsequent description of renal secretory mechanisms, and (5) toxicological advances in defensive methods against the poisons of gas warfare during World War I. A dedicated humanitarian as well, Starling served as Chairman of the Royal Society's Food Commission and directed efforts to alleviate wartime food shortages.

## Front Row Affliction

We could not ignore this sophomoric gem. This Figure was taken from an article entitled "Upon Inspection," (i.e. the first step in a physicial examination) in January of 1963. The legend gives the focussed history.

**FIGURE 8: The patient is a 19 year old conscientious, industrious medical student who developed the above-pictured lesion just before the beginning of final examinations. Culture revealed a prolific growth of E. coli. Diagnosis?**

*Diagnosis — as if you need to be told — Brown Noser. Some stereotypes never change.*

## Toronto: Canada's Cardiac Capital

The contributions from medical faculty and staff at the University of Toronto to advance the art and practice of cardiovascular surgery during the 1950's and 60's were remarkable. These accomplishments include: the first clinical use of heparin, innovative surgical corrections of inborn heart defects, and the development of the cardiac pacemaker. Here we profile some of the primary investigators who pioneered this rapidly changing field.

### Tinkering with the ol' Ticker

Historically, the heart was thought to be the epicenter of our emotions. Controversy thus engulfed the practise of cardiac surgery for it was believed that operating on this organ not only put the individual's physical health, but also their emotional health at risk. The following quote and excerpt were published originally in April, 1963 and reflect the time when tinkering with the ol' ticker was considered frankly unethical.

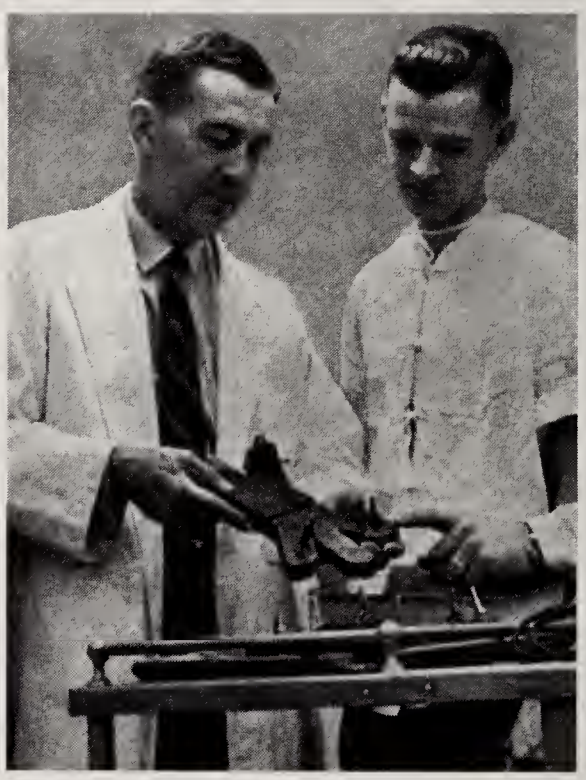
*"Paracentesis of pericardium is an operation which some surgeons would term a prostitution of the surgical art . . ."*

### Cold Hearted Doctors Save Lives

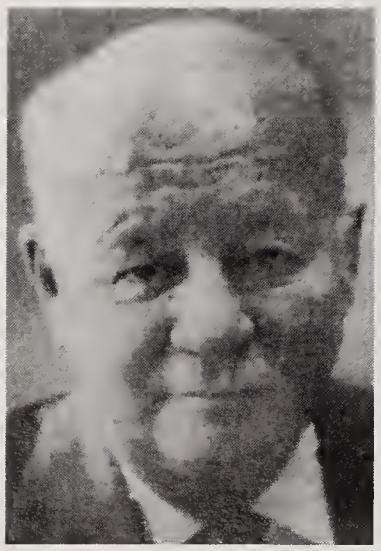
Hypothermia research by W.G. Bigelow and colleagues at the Banting Institute resulted in the first successful open heart surgery in 1950. Bigelow began four years of research following his mantra, *Cool the whole body, reduce the oxygen requirements, stop the circulation and open the heart.* Hypothermia experiments also lead to the development of the first pacemaker in 1951. The introduction of transistor circuitry allowed for smaller pacemakers in 1959. Since then, pacemakers and heart surgery have saved and improved countless lives.

### Myocardial Magicians

**Gordon Murray** *(1894-1976)*, pioneer in the use of the artificial kidney. He graduated from the University of Toronto in 1921. Dr. Murray was the first to use heparin clinically as an anticoagulent and developed and introduced the first successful artificial kidney in North America in 1946. He was a pioneer in cardiac surgery and was the first director of research at the W.P. Caven Memorial Research Foundation (later the Gairdner Medical Research Foundation).



*Dr. Bigelow with medical student*



**William Thornton Mustard** *(b. 1914)*, orthopaedic surgeon. He graduated from the University of Toronto in 1937. From 1948-64, he was head of Orthopaedic Surgery at the Hospital for Sick Children and was head of cardiovascular surgery from 1964-76. An innovative surgeon, he was the first to use prosthetic glass tubes in wounded arteries and in the repair of congenital defects in early infancy. His most important contributions were the development of the ileopsoas transfer operation and the Mustard atrial repair for children.

*"The patient's temperature reached 30°C. The superior and inferior vena cavae were totally occluded and complete circulatory arrest was produced. After three or four beats the heart emptied itself of blood. The right atrium was opened and by direct vision a small atrial septal defect was closed by means of a continuous running suture. A clamp was then placed across the incision in the right atrial wall, the tapes around the superior and inferior vena cavae loosened and the circulation restarted. During the entire procedure the heart continued to beat slowly but regularly . . ."*

## Culture and Sensitivity

Although the heart is often viewed as merely a site of pathology, it is also a metaphor for compassion and understanding. The following editorial was originally published in December, 1954, Volume 32, Number 2 and concludes this portion of *From the Archives*. This article reminds physicians and students to encorporate empathy and sensitivity in their daily practice.

# EDITORIALS

Not long ago a friend of ours was taken to the Emergency Department of one of our teaching hospitals for treatment of severe injuries and shock that she had suffered in an automobile accident. A small group of keen young men wearing white coats and "Dr. J. Doe" badges examined her and then withdrew several feet for a spirited discussion of the case. She overheard great differences of opinion expressed regarding diagnosis and treatment, and was seized by the very disturbing realization that her doctors were not equal to the situation. When one of them (older than the others) finally announced what was to be done, she received the decision with an uneasiness which persisted until someone told her that all the other "doctors" had been medical undergraduates.

Thoughtless students can cause sick people considerable discomfort. Most of us scrupulously avoid bedside expressions of horror or pity, or the use of such terms as "syphilis", "tuberculosis" and "cancer". But we may distress in subtler ways. In the incident cited, mere disagreement among her "doctors" disturbed the patient far more than the taboo words would have done. Sometimes, rather than confessing that we are only students, we attempt sage answers to the patients' questions. We occasionally leave his (or her!) jacket untied, bed cranked down, bed-table out of reach, and radio turned off. Frequently, having finished with the patient, we linger at the bedside for prolonged discussion which could as well be conducted elsewhere. The student who conscientiously warms his stethoscope-bell yet half-a-minute later coughs in the patient's face has created an uncooperative subject. All these things are unkind, unnecessary, and poor public relations.

Usually these sick people are available for us to practise our arts upon because they are unable to pay for more privacy—let's not make needless discomfort their penalty.

W. H. S.

## Acknowledgements

We would like to thank Dr. Edward Shorter and the University of Toronto Archives for their generous help.

# An Introduction to Medical Informatics

Howard Strasberg, MD

A 59-year-old male comes into your family practice office, three days after discharge from hospital following his first myocardial infarction. He has been symptom free since discharge. He has difficulty answering your questions about his course in hospital, test results, current medications (which he did not bring), and even exactly why the cardiologist told him to see you today. You don't worry about this lack of information, however, because you have a computer on your desk to help you out. You are no longer practicing in an era of illegible paper charts and 14-day delayed hospital discharge summaries. Your computer links to the hospital information system, and you discover that the patient had an inferior MI ten days ago, treated with streptokinase. Coronary angiography revealed mild irregularities in the right coronary artery. The patient was sent home on atenolol, ASA and nitroglycerin spray prn. You review the blood test results from the hospital, which include a total cholesterol of 5.1 mmol/L and an LDL of 3.8 mmol/L. Your decision support system recommends that the patient be started on lipid lowering therapy, quoting the CARE[1] study. You review the study yourself with the click of a button, discuss the benefits and risks with the patient, and you decide to begin therapy.

The above scenario illustrates some of the promises in the field of Medical Informatics. If you have never heard of this field, you are not alone. Many health care professionals, including many physicians, react with a blank look of incomprehension when this term is mentioned. This article will introduce you to Medical Informatics, and its key role in the practice of medicine.

Medical Informatics is defined as *the scientific field that deals with the storage, retrieval, sharing and optimal use of biomedical data, information and knowledge, for problem solving and decision making.*[2] The practice of medicine relies heavily on information, that is, having the right information in the right place at the right time to make decisions about patient care. Two general types of information are required - biomedical data and biomedical knowledge. First, one must have the patient's biomedical data. This data includes items such as the patient's medical history, symptoms, medications, allergies, physical exam findings and laboratory test results. Together this data forms a database for the patient. Clinicians are generally quite familiar with the difficulties that arise in decision making when this data is not available, as is too often the case. For example, patients frequently arrive in the emergency department with a potentially serious presenting complaint, but data surrounding recent tests and consults are unavailable. This situation leads to delays while attempts are made to obtain this data and/or tests are repeated. The second type of information required is biomedical knowledge. New knowledge is being generated at a rate that makes it impossible for clinicians to keep up with the literature. A computer tool is therefore required to allow clinicians to access this biomedical knowledge as the need arises. One can see therefore the significant advantages of Medical Informatics tools designed to provide access to biomedical data and to biomedical knowledge. The field of Medical Informatics, however, also involves the merging of these two areas to provide decision support. In the scenario above, the computer system integrated the biomedical data (cholesterol results) with the relevant biomedical knowledge (CARE results) to come up with a recommendation for therapy.

From its definition above, two things become clear about Medical Informatics - first, it is a broad field, and second, it is a scientific field. Many research areas are uncovered as one thinks further about the implementation of the ideas outlined above. The table below outlines some of the domains of Medical Informatics, along with selected research issues.

The wealth of research issues in this field, as well as the unique requirements for training professionals in this field, emphasizes the need for Medical Informatics to exist as an academic discipline.[4] Academic medical centres must include provisions for

| Medical Informatics Domain | Research Issues |
|---|---|
| Expert Systems and Artificial Intelligence | How do we integrate a biomedical knowledge base with a patient database to help clinicians make a diagnosis? |
| Medical Decision Making and Guidelines | How do we integrate a biomedical knowledge base with a patient database to help clinicians make decisions about management? |
| Clinical Epidemiology | How do we study new tests and treatments, and how do we critically evaluate new literature as it appears? In other words, how do we continually update our collective biomedical knowledge? |
| Knowledge Acquisition | How do we translate biomedical knowledge into a knowledge base that the computer can understand? |
| Data Acquisition | How do we get the patient data into an electronic patient record system? How might tools, such as templates, voice recognition and pen-based computing, help us accomplish this important task? |
| Standards and Vocabulary | How can biomedical data be represented in a standard fashion, so that different systems can communicate with each other, to facilitate patient care and research? (e.g. ICD9 is a vocabulary standard; DICOM is an imaging standard) |
| Human-Computer Interaction | How can the human-computer interaction be optimized so that busy clinicians will actually use the tools that are developed? |
| Telemedicine | How can we use audio, video, communications and information technology to provide remote consultations for patients and physicians who are without immediate direct access to the specialists they need? (e.g. radiologist reporting films taken at a remote location; dermatologist looking at a video of a skin rash) |
| Privacy, Security and Confidentiality | How do we protect patient confidentiality when we start to talk about storing and transferring patient information electronically? (e.g. audit logs of accesses to electronic records, encryption of data, authentication of users) |
| Bioinformatics | How should we use information technology to help us manage the wealth of information being generated in the exploding field of molecular biology? (e.g. The Human Genome Project) |
| Medical Education | How do we incorporate Medical Informatics into undergraduate, postgraduate, and continuing medical education? |
| Imaging Informatics | How do we improve the storage, retrieval, sharing and management of medical images? |
| Bibliographic Retrieval | How can we improve methods for retrieving information from databases such as Medline, such that the information needed is available in a timely fashion at the point of care? |
| Evaluation | We must evaluate the Medical Informatics tools that are being designed. Are clinicians satisfied with the tools? Do they result in improved quality and efficiency of patient care? Do they result in cost savings? (e.g. a meta-analysis of several studies demonstrated that computer-based reminder systems improve preventive care in the ambulatory setting) |

Medical Informatics to exist as its own academic unit, and not just as an area in which a few faculty dabble in their spare time while working primarily in other departments. With appropriate academic attention, research in this field will continue to grow, leading to improvements in all areas of medicine.

Whether you are a student, resident, community or academic physician, or other health care professional, you are encouraged to think about how your field could be improved through the use of Medical Informatics. You might further consider how Informatics might be included in your clinical, research, teaching and learning agendas.

If you think you might be interested in Medical Informatics as a career, you can find a list of Medical Informatics Training programs by starting at this web address: *http://amia2.amia.org/lkedtr.html* (American Medical Informatics Association). Usually the training programs involve a fellowship or a graduate degree in Medical Informatics. People trained in Medical Informatics may find careers in academia, hospitals and industry.

The 21st century is around the corner. Medical Informatics will be without doubt an integral part of the practice of Medicine. Will you be ready?

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# Medicine and the Palmtop

Jeremy Theal, BSc. (9T9)

*Smaller and more portable than a laptop computer, yet capable of many of the same functions.* This is perhaps the best way to describe the world's newest family of computers, the *palmtop*. These tiny devices rest in the palm of the user's hand, weigh less than half a pound and have batteries that last three to eight times longer than laptops. Palmtops can be used for word processing, database or spreadsheet functions, as well as Internet access, day planning, route planning and countless other applications. Additionally, palmtops are designed for connectivity with a desktop computer. Thus, it is possible to transfer PC and Macintosh files onto a palmtop and read or edit them on the go.

The advent of the *palmtop computer* has already had a significant impact on the field of medicine. Successful study and practice of medicine requires the quick recall of facts from a vast body of knowledge while in clinical situations. Previously, computers had a limited ability to provide this information, since they were not portable enough to accompany clinicians on ward rounds or emergency call. With the advent of the palmtop, however, this has all changed. Palmtops are presently capable of carrying upwards of 30 megabytes of information — the equivalent of about 30 paperback novels — in a package that is smaller and lighter than a single paperback. This considerable carrying capacity allows storage of large electronic databases of clinical information, which can be searched for facts relevant to a patient's case while at the point of care. For example, a young child may present to the Emergency Department with a limp, for which the clinician is unsure of the differential diagnosis. Searching a palmtop pediatric database may quickly provide the clinician with the relevant information (Figure 1).

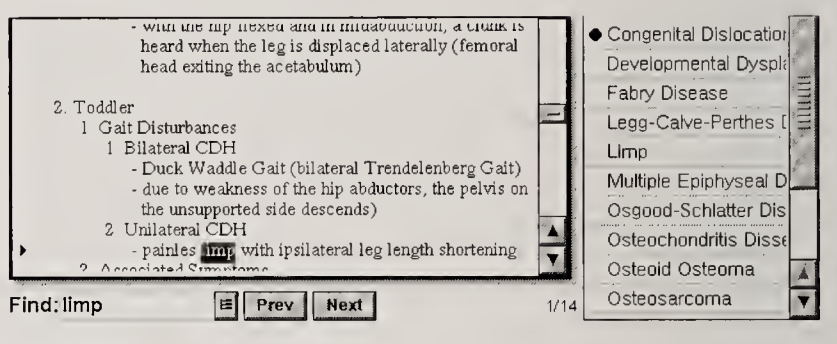
- with the hip flexed and in adduction, a clunk is heard when the leg is displaced laterally (femoral head exiting the acetabulum)
2. Toddler
1 Gait Disturbances
1 Bilateral CDH
- Duck Waddle Gait (bilateral Trendelenberg Gait)
- due to weakness of the hip abductors, the pelvis on the unsupported side descends)
2 Unilateral CDH
- painless limp with ipsilateral leg length shortening
Find: limp
Prev
Next
1/14
Congenital Dislocatio
Developmental Dyspl
Fabry Disease
Legg-Calve-Perthes
Limp
Multiple Epiphyseal D
Osgood-Schlatter Dis
Osteochondritis Diss
Osteoid Osteoma
Osteosarcoma

FIGURE 1. *Searching for diseases involving "limp" on a Psion Series 5 Pediatric database. Records matching the search-word are displayed as a menu on the right, and the contents of each record are displayed on the left.*

Palmtop databases have many advantages over reference books for on-the-spot clinical practice. First, they are much easier and faster to search for information, since the computer searches every word in the database for the required information instead of searching only the index. In addition, such databases are cheaper and faster to update – for example, you can simply download a free or inexpensive update from the Internet, rather than waiting 2-3 years to pay full price for the next printed edition of a book. Finally, due to the small size and weight of palmtops, these databases are now more portable than books. Digital databases are available for reference in any medical or surgical specialty. As well, extremely useful digital pharmacopeiae are also available, providing information about drug action, contraindications, and even dosages.

Medical students and residents may find it helpful to create their own database of items that they learn during the course of their training, as a replacement to a "little black

book". Not only does recording such information on a palmtop help cement concepts and facts learned, it also provides a way to rapidly access any previously taught material on-the-spot. Using a palmtop database to confirm or deny hypotheses while in patient-care situations (as opposed to later looking something up in the library) is tremendously useful to the student. Since the required relevant information is immediately available, it can be integrated more tightly with the current clinical experience in the mind of the student. The student also gains more confidence to make quick, on-the-spot decisions in the management of the patient.

Another significant application of palmtop computers is in the realm of patient record keeping. A new breed of software has evolved which allows a palmtop user to record, recall and print any detail about a patient's identifying data, history, physical examination, laboratory tests, investigations and treatments (Figure 2). Sophisticated versions even allow billing information to be entered. To save time during input, some of these programs allow the selection of terms from standardized menus containing the most common details of history, physical examination, laboratory tests and treatments. Drug information can be a snap to enter by choosing from a list of common drugs, routes of administration and dosages.

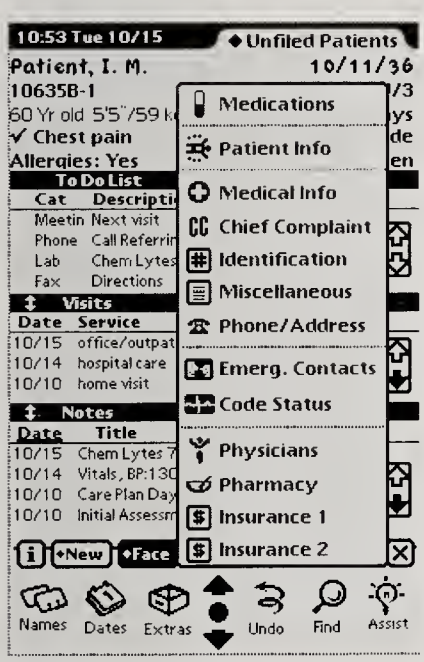


FIGURE 2. *The Virtual Intern 8 for the Newton series of handheld computers allows one to track every aspect of a patient's hospital stay.*

Currently, patient record-keeping software does not integrate well between palmtop computers and hospital computer systems. Thus, at present, entering patient information on a palmtop is strictly for the convenience of the palmtop user. However, a number of test hospital sites in the United States are developing patient record-keeping systems that include palmtops as an integral part of daily chart management. Preliminary results from these pilot projects indicate that eventually, doctors may use palmtops to carry the hospital's "virtual chart" for each patient in their care. The chart will be updated on the palmtop as the doctor goes about his or her day and synchronized with the hospital's computer system using docking stations or infrared beams. During the synchronization process, all orders from the physician's palmtop will be sent to the proper hospital departments and test results for the physician's patients will be transmitted from the hospital's computers to the palmtop. While a system like this is enormously complex both technically and organizationally, potential gains in efficiency from such a system indicate that implementation is advisable despite obstacles that may be encountered along the way.

The array of palmtop hardware currently on the market is almost as diverse as the available medical applications. Choosing a palmtop system is a difficult task and beyond the scope of this article. However, the most popular palmtops today include: the Newton, such as the MessagePad 2100; Windows CE products from Hewlett-Packard, Casio, NEC, and Phillips; the Pilot series from US Robotics (which includes the popular PalmPilot); and Psion, which sells in Series 3c and Series 5 models. Choosing between these systems is a matter of personal preference, since they differ in price, size and weight (very important considerations for a portable computer), available software, mode of input (keyboard or pen-based handwriting recognition), operating system and memory capacity. Many offer special features, such as add-on memory cards and modems to allow Internet access.

Palmtop computers, by setting new standards in portability, processing speed and storage capacity, have already demonstrated considerable capacity to provide assistance to the physician at the point-of-care. The rapid pace of computer hardware advancement means there is tremendous potential to develop future portable medical applications of even broader scope and greater utility. Indeed, palmtops are poised to become permanent tools in the arsenal of tomorrow's physician.

# Stedman's Plus 5.0, CD-ROM

Grant Chen, BSc. (0T0)

The medical and computer worlds have both advanced at a rapid pace in recent years. So much so that it comes as no surprise that advances in the computer world have fueled new medical achievements. There is no doubt that the most widely used computer application in the scientific community is the word processor. It is the word processor that medical and health professionals use to transcribe research papers and various medical reports. In addition to simplifying editing, many word processors include tools such as a spellchecking dictionary, thesaurus and even a grammar checker. This boon for word processor users is enhanced further by Stedman's Plus Spellchecker 5.0, which is an excellent medical/pharmaceutical spellchecker.

Stedman's has had a strong reputation for years for producing a good concise medical dictionary for health professionals, which was published in its 26th edition in 1997. With Stedman's Plus Spellchecker on CD-ROM, now in its 5th edition, Stedman's has continued the tradition of excellence in providing medical and health professionals with an excellent resource tool.

Stedman's Plus Spellchecker fills a void that many medical and health professionals find in the spellchecking capabilities of word processors. How many times have medical professionals, writing up case reports or research papers, had to constantly press the "ignore" button whenever the current spell checker found a common medical or scientific term? Stedman's Plus Spellchecker fills in the gaps that regular spellcheckers have in their lexicon. In addition to medical terminology, Stedman's Plus Spellchecker includes a pharmaceutical dictionary that contains updated trade and generic drug names drawn from the PDR® Generics™ database and current medical literature. For example, when using the names of ACE inhibitors, the spellchecker will accept both the generic name, 'enalapril,' and the trade name, 'Vasotec.'

The spellchecker is simple to install and is compatible with most of the major word processing programs (Microsoft Word, Lotus AmiPro/WordPro, WordPerfect 5.1 and up). The power behind Stedman's is that it is constantly being updated. The most recent release (version 5.0) contains a lexicon updated in consultation with its' registered users and includes new terminology from *The International Dictionary of Medicine and Biology*. This extensive lexicon helps the user avoid the frustration that comes with constantly having to add new medical terminology to a supplementary dictionary. The spellchecker is so simple to use that once it is installed, the user will not even know that it is in action as it acts in conjunction with the regular spellchecker. The next step in enhancing the user-friendliness of the Stedman's repertoire could possibly be to add a thesaurus to give the writer more options for alternative word usage.

In addition to the program itself, the User's Guide is an excellent resource for those users who are interested in more advanced applications such as customizing spellchecking macros, dictionary chains (used with add-on spellcheckers that are specialty-specific), and even networking between different versions of the same word processor (useful on a network).

Stedman's Plus Spellchecker is ideal for medical and health professionals who write reports containing medical terminology. In addition, it can also be used by secretaries, researchers, lab technicians or anyone who uses terminology related to new medications or technologies.

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**C : \ Quick \ Reference \ Review**
**Stedman's Plus 5.0, CD-ROM**
List Price: $99 (US)
Williams & Wilkins, Baltimore, MD
http://www.stedmans.com

System Requirements:
Platform: Hybrid (Windows/Mac)
Hardware Requirements: Requires 1MB free hard disk space; CD-ROM drive.
Rating (out of 5): ★★★ 1/2

# Principles of Medical Pharmacology, Sixth Edition

Reviewed by Sean Wharton, BScPhm, PharmD. (0T1)

Written by: Harold Kalant, Ph.D and Walter H.E. Roschlau, MD
Oxford University Press, 1998
Pages: 957

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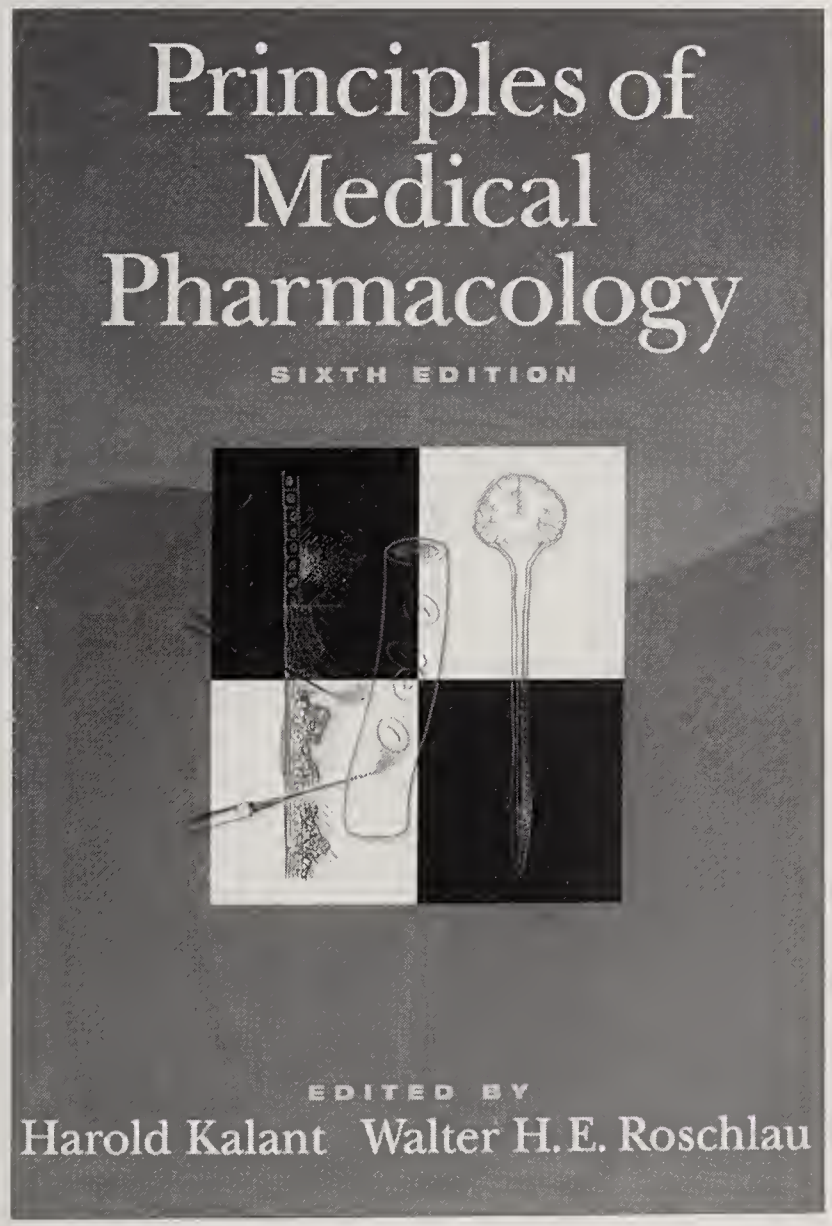
|---|---|
| Overall Rating: | Average to good. |
| Strengths: | Good breadth, covers the basics to intermediate complexity |
| Weakness: | Poor diagrams; clinical cases at the beginning of each chapter are not useful |
| Audience: | Appropriate level for undergraduate students and good reference for clinicians |




This is the sixth edition of a very well respected and internationally referenced textbook on medical pharmacology. From its inception in 1975, as a compilation of helpful lecture notes from the Pharmacology Department of the University of Toronto for its students in medicine, dentistry and pharmacy, this textbook continues to be an essential source for students newly introduced to the field of pharmacology, and is a helpful reference for practicing clinicians. This text also contains adequate detail for practicing clinicians to use to refresh themselves on the pharmacological aspects of the major groups of drugs. There are few textbooks capable of spanning such a large audience.

Undergraduate students with limited knowledge of pharmacology are guided through the first few chapters which introduce them to pharmacological terminology and physical chemistry relating to pharmacokinetics and pharmacodynamics. What the initial chapters lack is an explanation of the approach to pharmacological application in clinical settings. Examples such as aminoglycoside monitoring and improving patient compliance with appropriate dosage regimens should have been used to introduce students to clinical pharmacology. Kalant inaccurately describes the responsibilities of pharmacy and pharmacists in several instances. He narrowly discusses the science of pharmaceutics and generalizes this to all of pharmacy, when in fact this is an area in which few pharmacists practice. Kalant carries this inappropriate characterization even further by failing to mention the role of physicians and dentists in the therapeutic application of

pharmacology. Physicians must be aware of drug half lives when deciding on the most appropriate regimens for patients; they must also be aware of drug metabolism and clearance to avoid drug-disease interactions, and drug-drug interactions. These clinical aspects are the final stages in the intense research that is involved in pharmacology, yet there is little recognition of how therapeutic decisions are made by clinicians. This would not be an issue if this book was intended for the pure pharmacologist, but it is intended for clinicians.

Kalant plainly states that this is a textbook of pharmacology rather than therapeutics, but the text would be much improved if there was a chapter dedicated to therapeutic application, demonstrating how the knowledge in this text is to be used clinically.

A question that should be asked before anyone spends money on a new text is, what does this new edition have to offer compared to the previous edition?

1. This text is well written as a pharmacology textbook. It has been updated to include 4 new chapters, totalling 75 in all. One of these new chapters, by Jane Mitchell, which reviews second messenger signalling, is a well written basic science overview. Of the 75 chapters, 31 have included new authors. The editors have recruited experts in the fields, including Gideon Koren, an expert in paediatric pharmacology, and Neil Shear, well known for his work in adverse drug reactions. These new authors bring up-to-date information to these areas.

2. Unfortunately this edition suffers from what appears to be economic downsizing as all the colourful, beautifully drawn diagrams, charts and tables from the previous edition have been replaced with two-toned lack-luster drawings. These drawings are not just unsightly, but the tables are difficult to read due to poor shading, which is the same colour as the text.

3. The editors have attempted to integrate some therapeutics into this text through the introduction of clinical cases at the beginning of each chapter. Unfortunately these cases serve no purpose as they are often long winded, and can only be appreciated after the chapter has been read. It would be more beneficial to ask simple clinical questions at the start or end of certain sections. These cases miss the mark.

Overall, the text may not be worth the money if you already have the 5th edition. If you do not have either edition, I highly recommend *Principles of Medical Pharmacology,* for basic pharmacology; however, in this case, the 6th edition may be the better one to buy, as you will benefit more from this edition's new information than from the 5th edition's artwork.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# So You Want To Be A Brain Surgeon?

Reviewed by Kevin Carter, MSc. (0T1)

Written by: Chris Ward and Simon Eccles
Oxford University Press, 1997
Pages: 182

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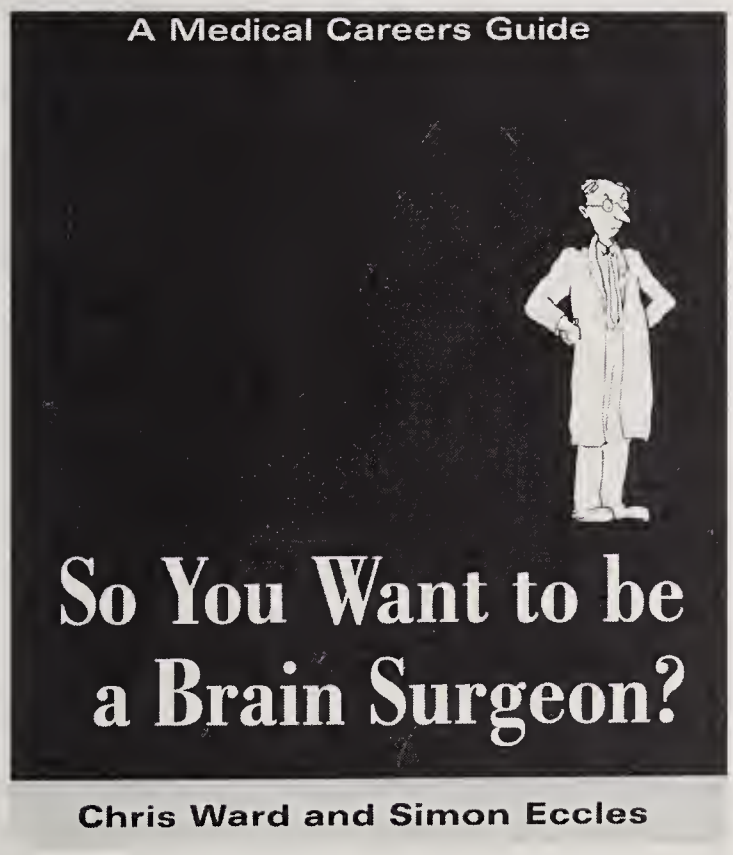
|---|---|
| Overall Rating: | Good |
| Strengths: | Quick reference tables, clear concise reviews of many specialties |
| Weaknesses: | Majority of information only relevant to the UK medical student |
| Audience: | Medical students |




One of the most attractive aspects of a career in medicine is the astounding opportunities and variety of jobs that are available to the medical doctor. However, choosing only one career path can be a daunting and sometimes fearful experience. *So You Want to be a Brain Surgeon?* was written to provide medical students with more information about the many specialties available to them, and in doing so, would help to produce doctors who are more satisfied with their career choices.

The title of this book does not reflect its actual content. The book provides information on a variety of specialties and subspecialties and is not a guide to becoming a neurosurgeon. Over eighty career paths are explored in this book and at least two pages are devoted to each field. The first page of each career choice is a somewhat in-depth look at the specialty, providing such information as a general job description, entrance requirements, and a course of action for interested students. Here, the book is very successful in giving an unbiased view of each career as well as providing useful insight into the pros and cons of the career. The second page for each specialty is a job summary table which is really the major strength of the book. The author uses a keyed rating system and visual tools (such as sad faces to depict stress and daggers to depict competitiveness). The rating system allows at-a-glance comparisons to be made between different jobs. This section provides you with such information as the hours of work per week, the competitiveness within the field, the stress levels, the number of hours on call, and the minimum, average, and maximum salaries. In other words, everything you wanted to know, but were afraid to ask.

Ward and Eccles lighten the content of the book by providing the myths and realities of each profession. For example, the myth about orthopedics is that it's full of "second row rugby forwards who are three times as strong as an ox and half as bright." The reality, according to the authors, is that orthopedics is full of "second row rugby forwards who are twice as strong as an ox and twice as bright." I often found myself flipping through the book looking solely for the authors' humorous outlook on various professions.

Unfortunately, this book was written by doctors in the UK, and is therefore directed at this population. Information such as the competitiveness, number of jobs available, and salaries cannot be translated into the Canadian health care system's statistics. The North American student is then left doing further research into these and other areas. In addition, some of the career options in this book are unique to the UK, just as there are Canadian specialties which cannot be found in this book. For North American students, this is the main downfall of the book, and one which cannot be overlooked.

Although there is no substitute for first-hand experience, *So You Want to be a Brain Surgeon?* can be an effective and entertaining tool in helping to make the most important choice in your medical career. This book should be purchased early in your medical school career, read, and then referred to as you progress and learn more about the many paths that a medical degree offers. If you have thoughts about practising overseas, this book could prove to be extremely helpful. However, even if you are planning a career in North America, this book provides insight into the many specialties that we are rarely exposed to and therefore rarely consider. At $27.95, *So You Want to be a Brain Surgeon?* could be your smallest investment into your biggest decision.

# Medicine and the Internet. Introducing On-line Resources and Terminology (2nd edition)

Reviewed by Martin Jugenburg, BSc. (OT1)

Written by: Bruce C. McKenzie
Oxford University Press, 1997
Pages: 353

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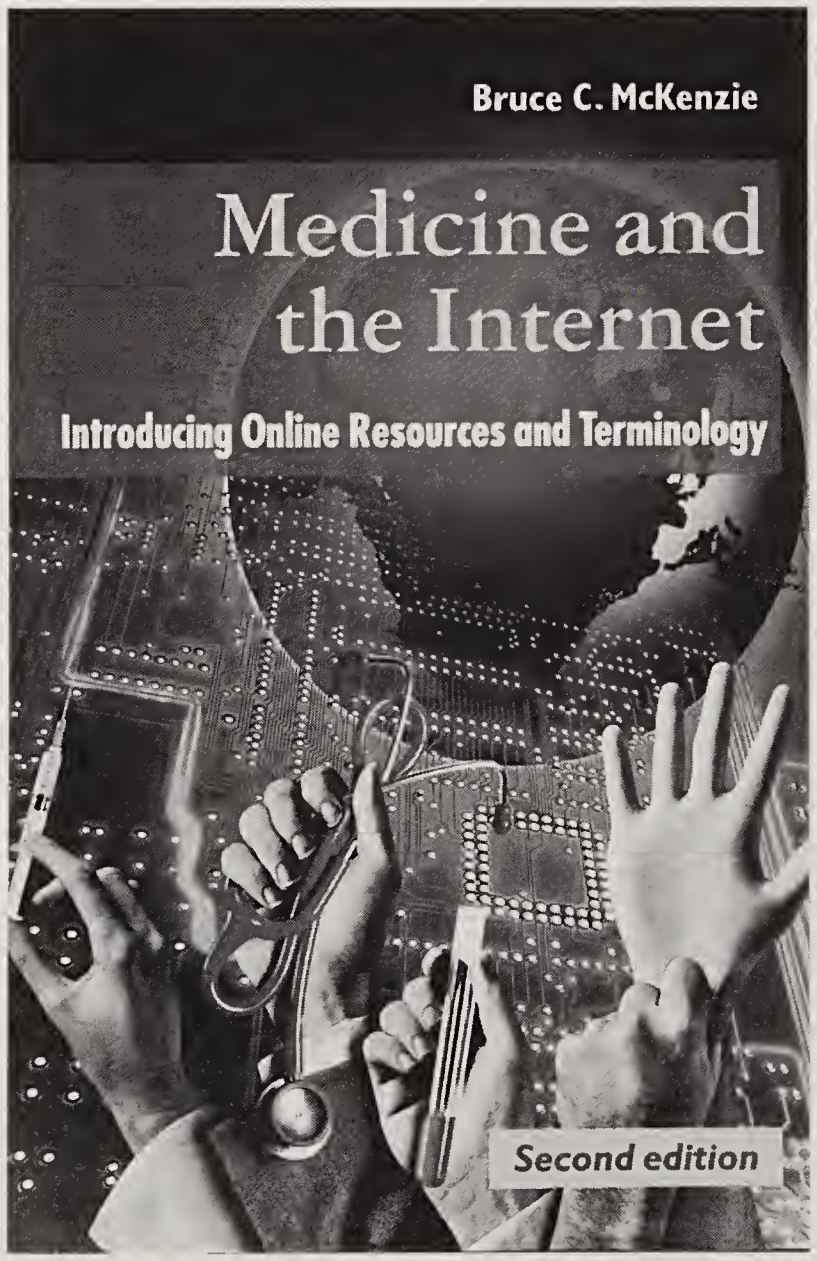
| Overall Rating: | Good |
| Strengths: | Discusses medicine-related topics not found in other books |
| Weaknesses: | Outdated |
| Audience: | Medical professionals and students |




The first impression one gets from looking at the cover of this book and its list of contents is that of a sophisticated book dealing with issues unique to medicine which are not found in the average Internet text. Although it remains unquestionable that McKenzie has aimed this book at medical professionals and students, one starts to wonder how efficient and sophisticated this text really is. Compared with other books dealing with the Internet, this one is a middle-of-the-pack kind of text.

However, it stands out because of its relevance to the medical field, as it contains references to numerous excellent medically-related websites. What makes this book truly stand out are its sections on issues such as copyright, plagiarism, and referencing Internet sources of information. These issues are applicable today, and they are things I have wanted to know about for quite a while. The author also discusses future uses of the Internet in medicine by using several relevant examples, and explaining how doctors can become information providers on the Internet. Other medically relevant topics that set this text apart from most other Internet books include health services on-line, electronic journals, medical education over the Internet, and electronic communication with patients, among others. Electronic communication with patients is a crucial topic since it will be a part of everyday life once today's medical students graduate. Although this section is short, McKenzie has done a good job of discussing both the advantages and disadvantages of email in doctor-patient communications, as well as data security.

The book also has a corresponding website with updates, meant to keep the book up-to-date. Unfortunately, the updates are few and superficial, the latest being from the winter of 1997. Hoping to get more up-to-date information from the site, I registered with it, only to be disappointed as I found no new updates available to registered users.

Reading the book, I noted three main weaknesses: 1) it is out-of-date; 2) it is written like an old-style computer book; and finally, 3) it is primarily aimed at a British audience.

Any book written about computers, especially about the Internet, will start to become obsolete immediately from the date on which it hits the store shelves (if not earlier). This book is no exception. Published in February 1997, it seems to transport the reader back in time by at least two or three years. Several of the Internet services discussed, such as Archie, Veronica, Gopher, and others, although still present, have almost completely lost ground to the new standard of the Internet world - the World Wide Web (www). Also, due to the hypervariable nature of the Internet, numerous links to webpages and documents on the Internet mentioned in the book are slowly being discontinued. Several times, I needed to search through the servers to find documents to which the book was referring.

Compared with other Internet books on the market, McKenzie's book seems to be based on the old style of computer books. It is heavy on text, while being very light on diagrams and screen-shots. The lack of colour text and diagrams makes the book appear a bit dull and monotonous. Skimming through it, there is nothing to catch one's attention, nothing to distinguish the essential sections from those which are not so important, thus leaving the reader feeling "congested" and overwhelmed. It was not until page 90 that the book actually introduced the Internet, and it was not until page 197 that McKenzie introduces the World Wide Web. And, getting to those pages was not easy reading. I was often left asking myself how useful some of it was. Instructions on connecting to the Internet, for example, went into detail that is irrelevant for busy professionals. Today, nearly all Internet providers give their customers proper connection software that will automatically set up everything.

Another weakness of this book is the fact that the author's target audience is British. Internet references to UK sites often remind the reader of this fact. Although the Internet is international, the reader is nevertheless often left wondering how relevant these resources are to anyone outside the UK.

The book may be beneficial to the novice and intermediate computer users in the medical field, with its explanation of computer basics, Internet access, and web browsing, but it lacks the simplicity of other books aimed specifically at "computer-challenged" individuals. Although the way it tackles the Internet and computers in general could be improved, its handling of medicine-related issues is good, and I am eager to see the updated version once it comes out. I recommend this book to an intermediate computer user familiar with the Internet, who is trying to explore its applicability to medicine.

# Endocrinology: Key Questions Answered

Reviewed by Chris McIntosh, MSc. (0T1)

Written by: John Laycock and Peter Wise
Oxford University Press, 1997
Pages: 323

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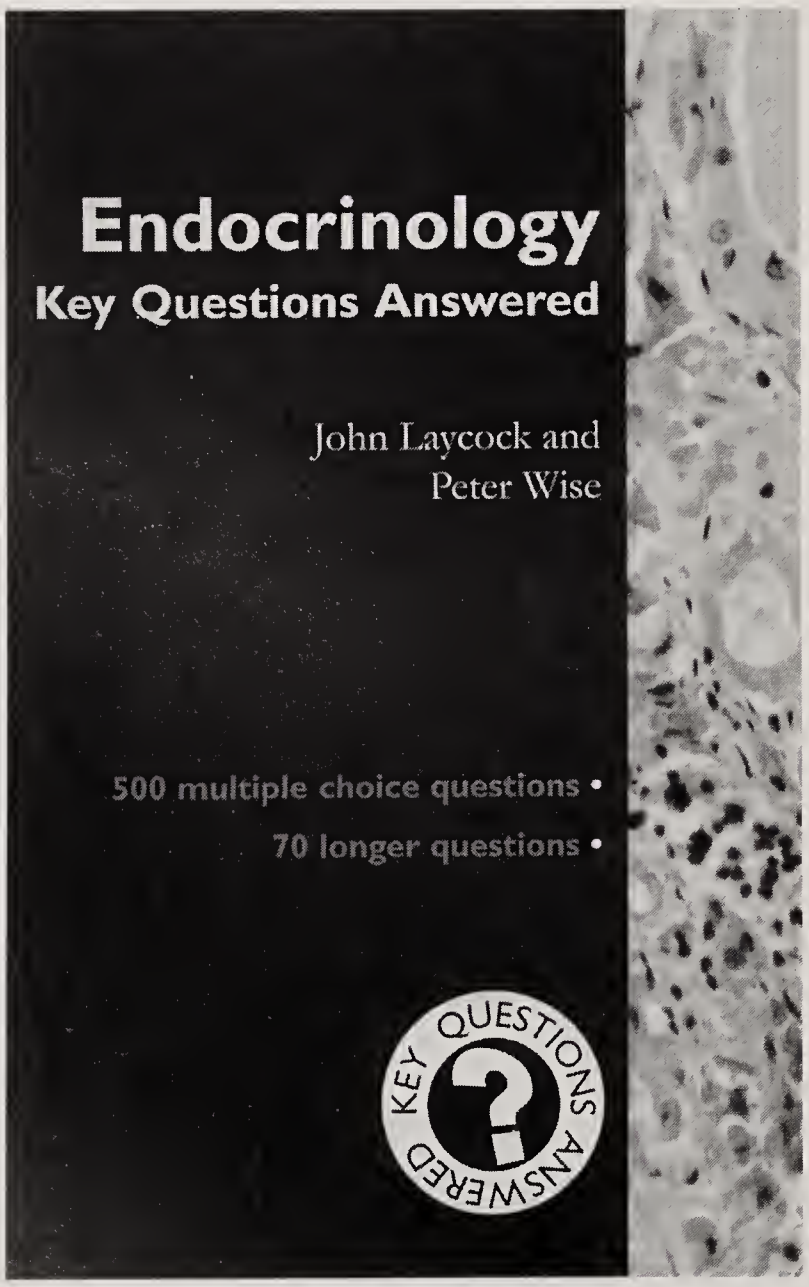
| Overall Rating: | Fair to Poor |
| Strengths: | Comprehensive, good clinical review section |
| Weaknesses: | Poor quality of diagrams, poor physiology section, poorly organized |
| Audience: | Medical students and residents |




*Question 1. You are asked to review an endocrinology study guide that consists of 500 multiple choice questions. Please select the most appropriate response.*

*a. Shout "No!" and run screaming from the room.*

*b. Fake hypoglycemic shock and escape as the editor is calling 911.*

*c. Ask "I get paid for this, right?"*

*d. A and B but not C.*

*e. C and D but not A.*

To begin with, I have to say that I am not a big fan of multiple-choice questions (MCQs). The increasing prominence of MCQs on university examinations stems from their cost-effectiveness, not from their efficacy in evaluating students' knowledge. So, I approached *Endocrinology: Key Questions Answered* with a bit of a skeptical air. Could MCQs actually be useful as a practical learning tool, or are they only good for learning how to answer more MCQs? As it turns out, Laycock and Wise manage to make the technique work in the clinically-oriented sections, but the rest of the book is a mess.

The book is divided into fourteen chapters. The first three deal with basic concepts in endocrinology, followed

by seven more discussing the major endocrine organs (adrenals, thyroid, pancreas, etc.). The final four chapters have broader themes such as growth and development, or lipid metabolism. Each chapter is then sub-divided into a physiology section and a clinical section, each of which has a group of MCQs, followed by a smaller number of short-answer questions (SAQs). The answers (with detailed explanations) follow each section of questions. As you might surmise, this endless sub-dividing into sub-sections makes for a lot of page flipping when you are trying to find the answer to a particular question.

In terms of the questions themselves, let me describe the physiology sections first. Here's an example from the section on male reproductive endocrinology:

P.6 Androgens

a. are 21-carbon steroids

b. are synthesized from the precursor cholesterol

c. are only synthesized by the Sertoli cells in the testes

d. are only synthesized in males

e. are transported in the blood mainly bound to sex hormone binding globulin

For each part of the question you must determine whether the statement is true or false. This in an unusual format for MCQs. Usually, you are instructed to choose the one statement of the five that is true (or false). Here there could be two true and three false, or three true and two false, or any other combination. Unfortunately, you are left to figure all this out for yourself; not even the preface, ironically entitled "How To Use This Book" tells you about this. Even more unfortunate is the fact that all of the Physiology MCQs have the same annoying "finish this sentence" format.

Thankfully, the clinical sections are more straightforward. Here's an example from the chapter on the pituitary gland.

C.7. A 25-year-old woman complaining of fatigue and amenorrhea is found to have a serum prolactin level of 3250 mU/litre (NR 50-450). Which of the following is/are consistent with this presentation?

a. The use of anti-depressants

b. Anxiety associated with imminent loss of employment

c. Primary hypothyroidism (Hashimoto's disease)

d. Prolactinemia

e. Pregnancy

I think the multiple-choice format works better in the clinical sections because it approximates the real-life technique of differential diagnosis. In the answer section, the explanations of each possibility are clearly worded and concise.

For both the physiology and clinical sections there are also some short-answer questions. These are generally good review questions, but the diagrams that accompany the answers are simply appalling. Perhaps, in keeping with the theme of the book, the authors meant to approximate the quality of a diagram that might be drawn by a student scribbling furiously to finish a question in the last five minutes of exam time. However, if we are meant to actually learn from this book, I think they could have spent the extra money for professional graphic design.

This book has potential, as it is a comprehensive guide to the essential topics in endocrinology, but I can't recommend it in its current form. Perhaps with some reorganization, some rewriting of the physiology section, and much improved diagrams, the second edition will be worth purchasing.

# Genes VI

Reviewed by Joyce So, BSc. (0T1)

Written by: Benjamin Lewin
Oxford University Press, 1997
Pages: 1260

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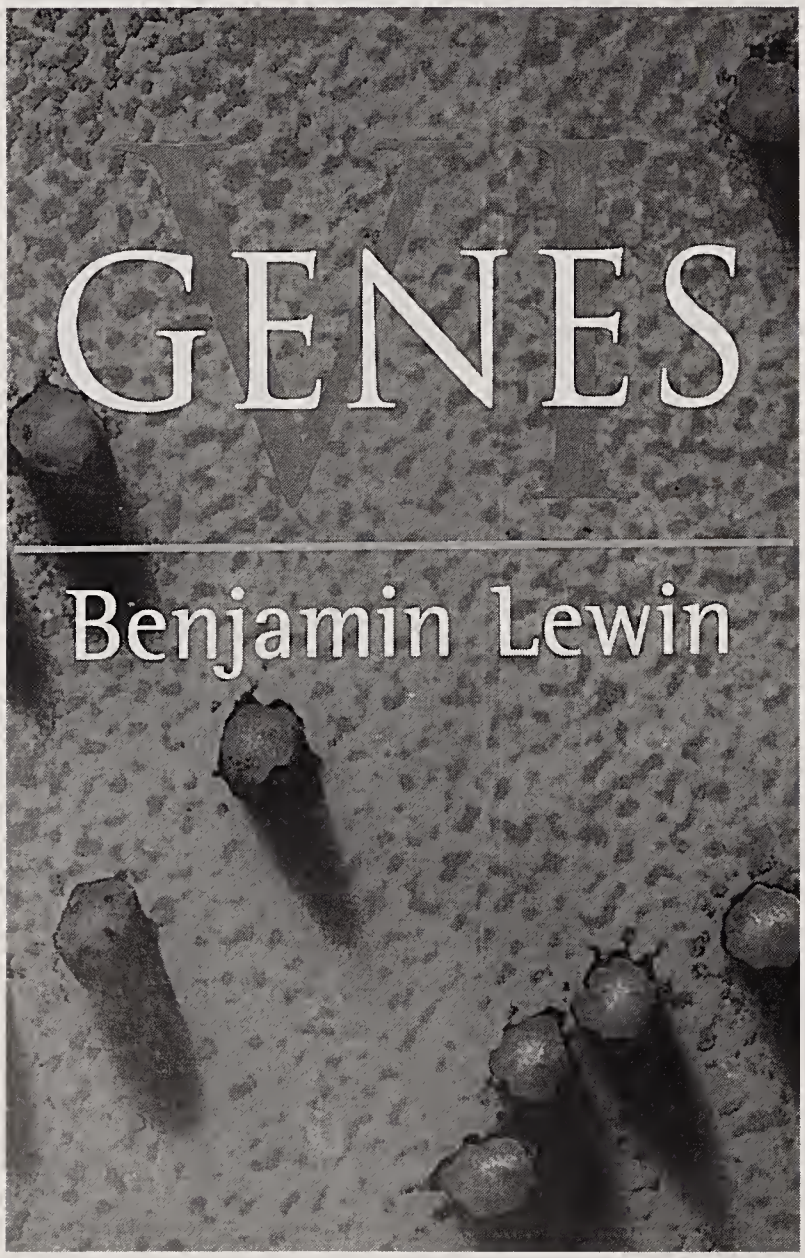
| Overall Rating: | Good |
| Strengths: | Clear, up-to-date, and comprehensive |
| Weaknesses: | Some topics not covered as well as others |
| Audience: | Undergraduate science students |




The field of molecular genetics and molecular biology is in a constant and rapid state of advancement and change. Thus, it is no simple feat that Benjamin Lewin has been able to compile such a current and comprehensive textbook as *Genes VI,* covering all the basic concepts, models, and systems necessary for a solid understanding of molecular biology.

Beginning with a simple, broad overview of the cell, Lewin gently eases the reader into genetics with a brief introduction to biochemistry and cell biology as they relate to the macromolecular cell. This gives the reader a good sense of the *big picture* before delving into more complex concepts and models. It is also a good reminder of basic terms, definitions, and concepts necessary for the understanding of simple biological processes (e.g. chemical reactions, bonding, enzyme catalysis, etc.), as well as cell structure and function.

The book is then divided into seven parts, taking the reader from the structure of DNA, through the intricacies of gene expression in prokaryotes and eukaryotes, to the complexities of cell growth and development. Each chapter begins with an introduction to outline major concepts to be discussed, and ends with a concise summary of the most important points. These summaries provide a good overview of *just the facts* without disruptive examples. Of course, the examples and related information presented in the chapters are often very helpful in understanding new concepts, and provide a practical basis for definitions and models.

The figures accompanying the text are generally clear, attractive, and helpful, although perhaps overly simplistic at times. Lewin's inclusion of crystal structures, 3-D models, light and

electron microscopy, and other "real" photographs aids in the visualization of certain concepts discussed in the text; more of these may have been helpful throughout the book. The legends accompanying the figures are, in many cases, too brief and could be expanded to explain the diagrams and figures more clearly and in greater detail.

With the ever-expanding and changing knowledge in molecular biology and genetics, it is difficult to determine how far to go and how much detail to include in discussing various related topics. In this respect, Lewin has managed to integrate a wide range of topics well. His concise, easy-to-understand writing style allows the reader to follow concepts readily and gradually advance into a more complex understanding of molecular biology and genetics. In general, each topic is covered thoroughly, with appropriate examples given, terms defined clearly, and the flow of information presented in a clear, logical manner. In some cases, however, it is apparent that the limit on information coverage was extended a little further, and some topics, such as protein localization, immune diversity, and protein trafficking, seem somehow out of place, or glossed over with insufficient explanation and detail. These topics, along with cell cycle and regulation (Part 7), amass a large volume of information which might be better left to providing some good introductions to these subjects as they relate to molecular biology and genetics. His provision of references for further reading at the ends of chapters is a useful guide for greater enlightenment on most topics discussed in each chapter.

One weakness of the book, as it pertains to medical students, is a general lack of material concerning the relationship between genetics and disease. This may be a conscious effort by the author to limit his book to straight concepts rather than applications, as even recombinant DNA technology is given only a light overview. With genetic engineering technology, such a prominent and essential tool in biomedical research today, it seems only appropriate that a more extensive discussion of the applications and implications of genetic techniques and concepts in medical research be included in any comprehensive text on molecular biology and genetics. Inclusion of this material would make this textbook more useful as an introduction to medical genetics, while it is currently an excellent aid to learning basic molecular genetics concepts.

In general, despite its few shortcomings, *Genes VI* is a well-written, complete and comprehensive overview of the important concepts necessary for a good understanding of molecular biology and molecular genetics. The information presented by Lewin provides a solid foundation for advanced learning in the field of medical genetics, and *Genes VI* is highly recommended to complement any basic undergraduate genetics course.

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*This advertisement was taken from the University of Toronto Medical Journal Archives, UTMJ Vol. 42, 1964*

# Clinical Immunology

Reviewed by Sandra L. Demaries, MSc. (OT1)

Editors: John Bradley and Jim McCluskey
Oxford University Press, 1997
Pages: 572

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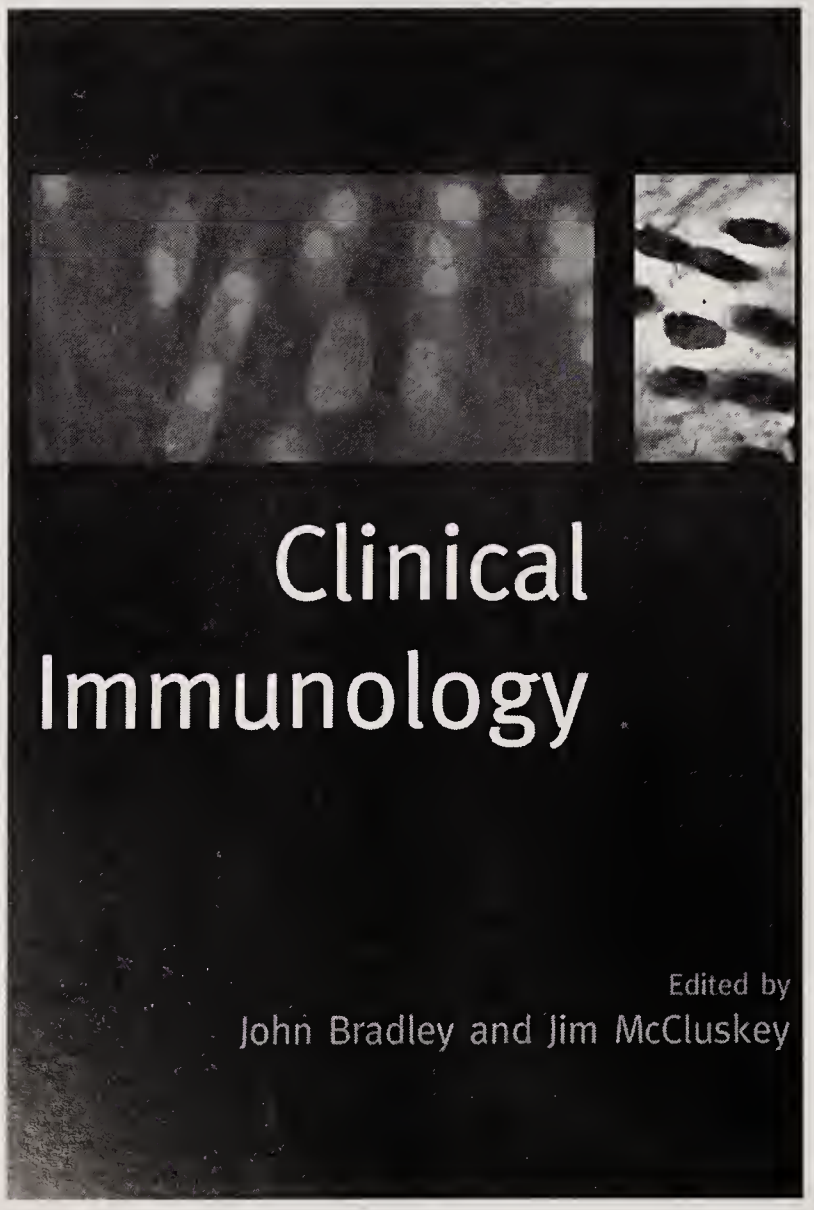
| Overall rating: | Very good-excellent |
| Advantages: | Wide scope, excellent diagrams and photographs |
| Disadvantages: | Expensive |
| Audience: | Medical students, and clinicians |




In the forward to *Clinical Immunology,* G.J.V. Nossal observes that since "immunology has the capacity to infiltrate itself into virtually every nook and cranny of medicine, clinical immunology has become quite a compendious discipline." This is indeed true. From transplantation medicine to HIV pathogenesis, understanding the function and regulation of the immune system is essential if many of the challenges to modern medicine are to be met. Attempting to produce a book which intends to serve as a primer for all fields of clinical immunology shows both courage and madness. However, editors John Bradley and Jim McCluskey have done just that with admirable results.

In total, 64 experts in a variety of fields have contributed concise chapters which attempt to bridge the cellular and molecular mechanisms of the immune system with the clinical phenotypes and treatments of the represented disorders. This in itself is an achievement; the gulf between what is going on in the basic immunology lab and the clinic remains wide. Through frequent reference to ongoing research, most contributors recognize the need to reconcile the lab and the clinic. Excellent quality colour diagrams, tables and photographs are present throughout, facilitating difficult concepts. Each chapter has a bibliography, although some seemed a little out-dated.

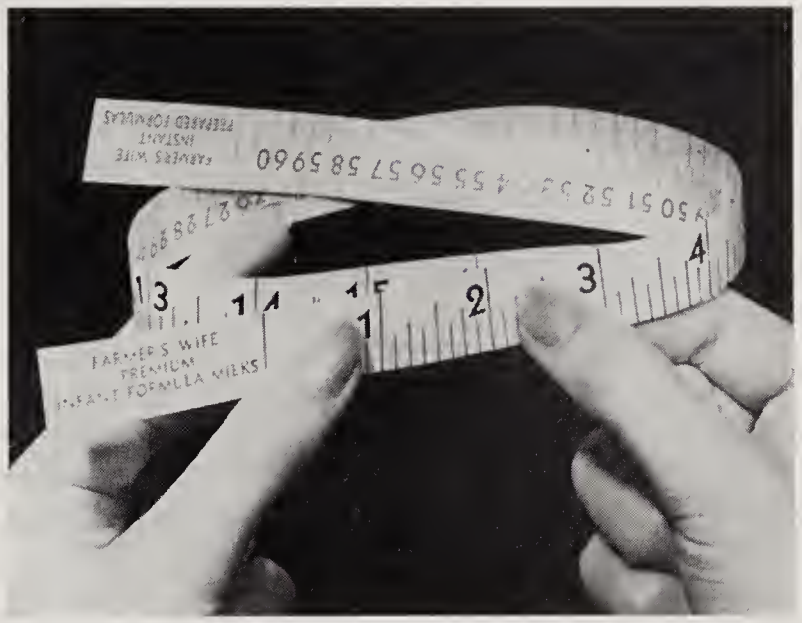
The book is divided into 8 sections: Immunodeficiencies,

Allergic Diseases, Immunological Diseases of Organs, Systemic Immunological Diseases, Transplantation, Immunology and Infection, Immunology of Malignancy, and Immune Interventions. There is no section dedicated to autoimmunity; instead, disorders which generally fall into this category are found throughout.

Of interest, in such a compilation is how 'big-name diseases' such as HIV or cancer will be treated, given their complexity. At 30 pages, the chapter on HIV infection in the Immunodeficiency section is the book's longest. This chapter dedicates approximately five pages to the epidemiology and molecular biology of the virus, eleven pages to the host response, immune pathology and diagnostic criteria for HIV infection, and the remainder of the chapter to clinical manifestation and treatment of disease. There are several nice colour diagrams to help in the understanding of HIV genetics as well as many excellent quality photographs of the clinical manifestations. This chapter, like all others in the book, assumes a background in basic immunology and pathology. It seems appropriate that there is an emphasis on the clinical aspects of disease, since the clinician and medical student are the intended readers. To be sure, a more specialized clinician would also require much more detailed and current sources. However, as an intended overview for the less experienced, the chapter is successful at presenting a complex disease in a concise, effective manner.

The chapter entitled 'Cancer' in the Immunology of Malignancy section may mislead some. Given the chapter title, it seems rather short at eighteen pages. This chapter examines only the direct role of the immune system in cancer (e.g. MHC expression abnormalities on tumour cells or the role of cytokines in cancer). It is certainly well written and worthwhile, since the role of the immune system in cancer progression is essential in the overall understanding of the disease. It seems that this chapter suffers most from a rather vague and daunting title; the reader really doesn't know what to expect.

As with any compilation, there is some heterogeneity in the style and focus of each chapter. However, this is made up for by the convenience of having, in one book, concise overviews of so many diseases. Disadvantages? Expensive ($136) and too brief in some instances. Overall, an excellent primer on the immunological basis of many diseases that are encountered routinely in the clinic.

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## Procedure for Submission

Contributions should be addressed to: The Editors, *UTMJ,* Medical Sciences Building, Room 2141, 1 King's College Circle, University of Toronto, Toronto, Ontario, M5S 1A8, Canada; Phone: (416) 946-3047. The paper should be submitted by an author, preferably the principal author, who should indicate in a covering letter:

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2. the exact address to which all related correspondence should be sent and the telephone and FAX numbers at which the author can be reached;

3. that neither the submitted manuscript nor any similar paper, other than an abstract of preliminary communication, has been or will be submitted to, or published, in any other primary scientific journal;

4. that all of the authors are aware of, and agree to, the content of the manuscript and that authorization has been given to use any information conveyed by either personal communication or release of unpublished experimental data;

5. three to six key words describing the paper, to assist in the selection of the reviewers.

**Original Submissions must include:**

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3. Computer diskette containing all the parts of the manuscript on **ONE** file. Refer to the following *Editing Process* section for more details.

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Tables should be on a separate page with a short title, and be numbered and referred to in the text. Column headings and descriptive matter in table should be brief. Vertical rules should not be used.

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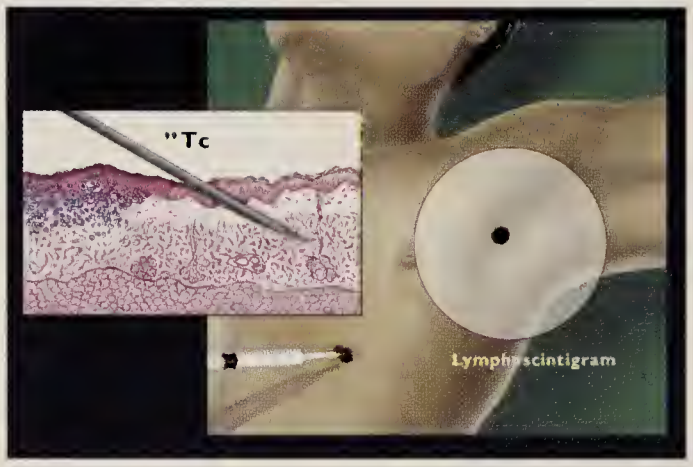


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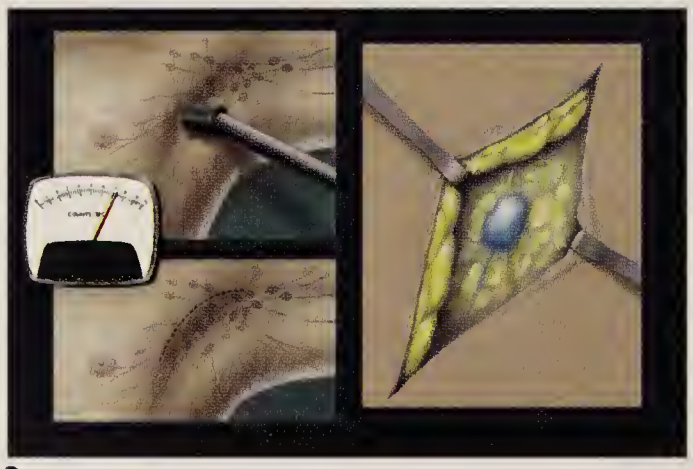

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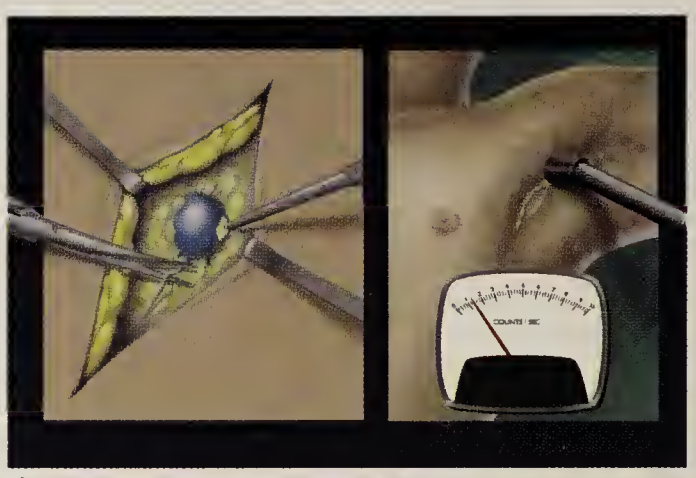

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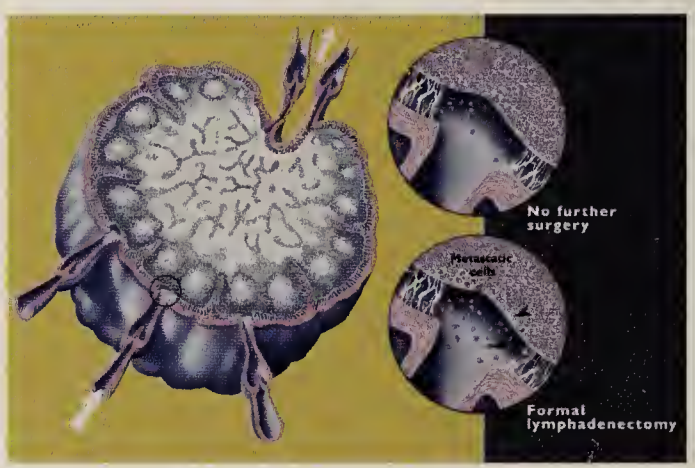


5

This series illustrates a sentinel node biopsy, which tests for metastasis of malignant melanoma to nodal basins. Intradermal injections of technetium-99 (1) and vital blue dye (2) proximal to the melanoma allow the lymphatic drainage pattern and the sentinel node to be identified (3). The sentinel node is biopsied (4), and a pathological examination for metastases (5) may necessitate a complete lymphadenectomy.

*Funded by the Canadian Society of Plastic Surgeons.*

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